Clinical trial results:
A prospective randomised open label trial of oxaliplatin / irinotecan plus fluorouracil versus oxaliplatin / irinotecan plus fluorouracil and cetuximab pre and post operatively in patients with resectable colorectal liver metastases requiring chemotherapy.

Summary

EudraCT number	2006-003121-82
Trial protocol	GB
Global end of trial date	18 December 2016

Results information

Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	4351

Additional study identifiers

ISRCTN number	ISRCTN22944367
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Southampton NHS Foundation Trust
Sponsor organisation address	MP138, Tremona Road, Southampton, United Kingdom, SO16 6YD
Public contact	Professor John Primrose, University Surgical Unit MP816, Southampton General Hospital Tremona Road Southampton SO16 6YD, 02380 796144, j.n.primrose@southampton.ac.uk
Scientific contact	Professor John Primrose, University Surgical Unit MP816, Southampton General Hospital Tremona Road Southampton SO16 6YD, 02380 796144, j.n.primrose@southampton.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	22 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2016
Global end of trial reached?	Yes
Global end of trial date	18 December 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary aim of the New EPOC trial is to determine whether the addition of cetuximab to oxaliplatin plus modified de Gramont or irinotecan plus modified de Gramont combination chemotherapy results in improved progression free survival when compared with combination chemotherapy alone in patients who do not possess a KRAS mutant genotype confirmed by laboratory analysis.

Protection of trial subjects:

Treatment duration and breaks
o Arm A (Control, OxMdG / IrMdG): These patients will receive 12 weeks of pre-operative and 12 weeks of post-operative chemotherapy dependent on cumulative toxicity, post-surgical performance status or because of patient choice to stop chemotherapy. Patients in this arm should continue on treatment with no more than a three week interval off treatment for any reason although the post surgical interval can be 6 weeks. The cumulative toxicity that is most likely to occur is the neuropathy associated with Oxaliplatin, which increases in incidence from about 12 weeks duration of therapy. If this occurs, patients may continue on the fluorouracil component of the regimen with dose increment. If the neuropathy resolves to < grade 1 the Oxaliplatin may be reintroduced cautiously at the investigator's discretion.
o Arm B: OxMdG / IrMdG plus Cetuximab: These patients will receive chemotherapy as Arm A above plus Cetuximab. Patients in this arm should continue on treatment with no more than a three week interval off treatment for any reason although the post surgical interval can be 6 weeks. Cetuximab will be continued if chemotherapy is stopped because of toxicity or patient choice, but should be discontinued on recurrence or unacceptable Cetuximab toxicity.

Background therapy:

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial
or
IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,lfolinic
acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.
NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly
Background of these drugs (from latest version of protocol 11Oct17):
Over 16,000 people die of colorectal cancer per annum in the UK (CR-UK Cancer Statistics, http://info.cancerresearchuk.org/cancerstats/reports/), most of whom die with metastatic disease. However the treatment of metastatic colorectal cancer is improving. The median survival has improved from about 6 months with best supportive care alone, through 10-12 months with 5FU regimens, up to 16-20 months in recent randomised trials including Irinotecan and/or Oxaliplatin and up to 27 months in other recent studies using targeted monoclonal antibodies. Recent data demonstrate increased response rates (31-56%), median progression-free survival (PFS, 6.5-9.0 months) and median overall survival (OS, 14.5-21.4 months) achieved with combination chemotherapy in first line therapy. The CR08 [FOCUS] trial compared 5 different schedules of administration of 5FU (using the modified de Gramont regimen) in combination with Irinotecan or Oxaliplatin in either first or second line therapy and has

the efficacy of first line combination chemotherapy.

Evidence for comparator:

Cetuximab (Merck KGaA, Darmstadt, Germany) is a monoclonal antibody to EGFR with activity in KRAS exon 2 wild-type colorectal cancer as a single agent. After promising phase 2 data, several studies assessed the benefit of cetuximab and panitumumab, a similar antibody, in combination with chemotherapy. In 2005, the COIN trial was initiated to investigate the addition of cetuximab to oxaliplatin and fluoropyrimidine chemotherapy in first-line treatment of advanced colorectal cancer. The New EPOC trial was begun as a rational extension to the COIN study, the EPOC study, and supportive phase 2 data, using much the same investigational strategies to assess whether the addition of cetuximab to oxaliplatin–fluoropyrimidine chemotherapy improved outcomes for patients with operable liver metastasis.

Actual start date of recruitment	26 February 2007
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 271
Worldwide total number of subjects	271
EEA total number of subjects	271

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)	138
From 65 to 84 years	133
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

271/288 required pts were randomised between 26Feb07-12Oct12. 14 pts were non-kRAS exon 2 wild-type (before amendment requiring kRAS testing), leaving 257 pts for the primary analyses. The study was closed to recruitment by the Trial Steering Committee on advice from the IDMC on 01Nov12 when the predefined futility criteria were met.

Pre-assignment

Screening details:

All patients were recruited from UK National Health Service hospitals. The study was approved by the South West Research Ethics Committee, and data were reviewed by the Independent data monitoring committee (IDMC). Written informed consent was obtained from all patients before random assignment.

Pre-assignment period milestones

Number of subjects started	823[1]
Number of subjects completed	257

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not meeting inclusion criteria: 402
Reason: Number of subjects	Patient/clinician choice: 104
Reason: Number of subjects	Other: 60

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: Number in pre-assignment period reflects the number of patients screened for the study as per the published CONSORT diagram. The worldwide number is the number registered to the trial.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Chemotherapy alone

Arm description:

Patients in this arm will receive either OxMdG or IrMdG:

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Arm type	Active comparator

Investigational medicinal product name	l-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

175 mg flat dose IV over 2 h

Investigational medicinal product name	d,l-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

350 mg flat dose IV over 2 h

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

Dosage and administration details:

concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h)

Investigational medicinal product name	5FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

5 minute bolus of 5FU (400 mg/m2; may also be given as a short 5 minute infusion or 15-30 minute infusion where this reflects local practice)

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

Dosage and administration details:

Irinotecan 180 mg/m2 IV over 30 minutes

Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Arm title	Chemotherapy and Cetuximab

Arm description:

Patients in this arm will receive either OxMdG or IrMdG, and Cetuximab (see Cetuximab dosage and administration details section):

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Arm type	Experimental
Investigational medicinal product name	l-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

175 mg flat dose IV over 2 h

Investigational medicinal product name	d,l-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

350 mg flat dose IV over 2 h

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

Dosage and administration details:

concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h)

Investigational medicinal product name	5FU
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

5 minute bolus of 5FU (400 mg/m2; may also be given as a short 5 minute infusion or 15-30 minute infusion where this reflects local practice)

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:

Patients will receive Cetuximab intravenous infusions at a dose of 500 mg/m2 to be administered over 2 hours and thereafter fortnightly infusions, or a loading dose of 400 mg/m2 followed by a weekly infusion of 250 mg/m2 for patients on the CAPOX regimen. Cetuximab is provided in ready use vials containing 5 mg/ml. Once removed from the vial, Cetuximab must be used within 8 hours if stored at room temperature.

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

Dosage and administration details: Irinotecan 180 mg/m2 IV over 30 minutes	
Investigational medicinal product name	Capecitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use
Dosage and administration details: capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly	

Number of subjects in period 1[2]	Chemotherapy alone	Chemotherapy and Cetuximab
Started	128	129
Completed pre-operative chemotherapy	99 [3]	103 [4]
Operated	113 [5]	108 [6]
Resected	108 [7]	100 [8]
Completed post-operative chemotherapy	59 [9]	62 [10]
Completed	128	129

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: Numbers in baseline period reflect the number of randomised patients. The worldwide number includes those registered but not randomised to a treatment arm.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Not all patients were included in each milestone as the milestones were set up to show how many patients received each intervention. Number completed includes all randomised patients followed-up.

Baseline characteristics

Reporting groups	
Reporting group title	Chemotherapy alone

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG:

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Reporting group title	Chemotherapy and Cetuximab

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG, and Cetuximab (see Cetuximab dosage and administration details section):

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Reporting group values	Chemotherapy alone	Chemotherapy and Cetuximab	Total
Number of subjects	128	129	257
Age categorical Units: Subjects			
Adults (18-64 years)	61	69	130
From 65-84 years	67	60	127
Age continuous Units: years			
median	65	64	
inter-quartile range (Q1-Q3)	59 to 70	59 to 69	-
Gender categorical Units: Subjects			
Female	47	37	84
Male	81	92	173

WHO performance status Units: Subjects			
WHO of 0	86	87	173
WHO of 1	42	39	81
WHO of 2	0	3	3
CEA level if raised (ng/ml) Units: Subjects			
CEA <= 5	45	42	87
5 > CEA <= 30	48	50	98
CEA > 30	31	34	65
Missing	4	3	7
Minimisation factor 1 (See description)			
Does patient have one or more of the following >=4 metastases, poor differentiation at biopsy, N2 disease?			
Units: Subjects			
Yes	68	71	139
No	60	57	117
Missing	0	1	1
Minimisation factor 2 (See description)			
Prior treatment with Oxaliplatin			
Units: Subjects			
Yes	11	15	26
No	117	114	231
Minimisation factor 3 (See description)			
Surgical Site.			
Units: Subjects			
Aintree	8	9	17
Barts	6	5	11
Basingstoke	12	10	22
Belfast	1	0	1
Bristol	20	22	42
Cambridge (Addenbrookes)	3	1	4
Cardiff	1	1	2
Edinburgh	1	0	1
Hammersmith	4	4	8
Hampstead	10	10	20
King's College	7	8	15
London	9	9	18
Manchester	0	3	3
Royal Marsden (London)	6	9	15
Nottingham	1	2	3
Pennine	9	10	19
Sheffield	11	10	21
Southampton	15	13	28
Surrey	4	2	6
Missing	0	1	1
Extension of the primary cancer Units: Subjects			
Absent (T1 or T2)	18	11	29
Present (T3 or T4)	107	109	216
Not Available	3	9	12
Lymphatic spread of the primary cancer			

Units: Subjects			
Absent (N0)	42	41	83
Present (N1 or N2)	83	78	161
Not Available	3	10	13
Presentation of Disease Units: Subjects			
Synchronous metastases	73	88	161
Non-synchronous metastases	55	41	96
Prior Treatment (see description)			
Prior treatment with Oxaliplatin/ Prior adjuvant chemotherapy for primary cancer			
Units: Subjects			
Yes (both)	10	12	22
Yes (adjuvant chemotherapy only)	15	9	24
Yes (oxaliplatin chemotherapy only)	1	3	4
No	102	105	207
Site of Primary Tumour Units: Subjects			
Right colon	22	20	42
Left Colon	23	30	53
Rectum	39	31	70
Rectosigmoid junction	19	20	39
Other	25	28	53
Number of lesions measured Units: Subjects			
1 Lesion	63	59	122
2 Lesions	34	30	64
3 Lesions	15	26	41
4 Lesions	8	9	17
5 Lesions	8	4	12
Not measured	0	1	1
Poor differentiation at biopsy Units: Subjects			
Yes	10	15	25
No	109	109	218
Missing	9	5	14
Planned backbone treatment			
Planned backbone treatment (using regimen received at cycle 1)			
Units: Subjects			
CAPOX	27	24	51
OxMdG	87	89	176
IrMdG	11	15	26
Missing	3	1	4
>3cm tumour diameter in at least one lesion at screening assessment Units: Subjects			
Yes	63	75	138
No	65	54	119
Extrahepatic involvement Units: Subjects			
Yes	3	6	9
No	125	122	247

Missing	0	1	1
Lymph node positive primary			
Lymph node positive primary (yes/no)			
Units: Subjects			
Yes	83	78	161
No	42	41	83
Missing	3	10	13
Status of primary tumour Units: Subjects			
Resected	119	110	229
Unresected	9	18	27
Missing	0	1	1
Number of metastases Units: Subjects			
1 to 3	103	97	200
4 or more	25	32	57
Time from primary tumour diagnosis to metastatic disease diagnosis (years), categorical			
Time from primary tumour diagnosis to metastatic disease diagnosis (years), categorical			
Units: Subjects			
<2 years	116	115	231
2 or more years	12	14	26
Plasma CEA level at the time of diagnosis of liver metastases			
Plasma CEA level (ng/ml) at the time of diagnosis of liver metastases			
Units: Subjects			
<=5	45	42	87
>5 to <=30	48	50	98
>30	31	34	65
Missing	4	3	7
Plasma CEA level at the time of diagnosis of liver metastases, binary			
Plasma CEA level (ng/ml) at the time of diagnosis of liver metastases, binary			
Units: Subjects			
>30	31	34	65
<=30	93	92	185
Missing	4	3	7
Time from primary tumour diagnosis to randomisation Units: Months			
median	4.3	3.5	
inter-quartile range (Q1-Q3)	2.6 to 17.5	2.4 to 11.4	-
Sum of the largest diameters of lesions on imaging			
Sum of the largest diameters of lesions on imaging (in mm), using the 5 largest lesions.			
Units: mm			
median	44.5	53	
inter-quartile range (Q1-Q3)	27 to 73	30 to 83	-
Time from metastatic disease diagnosis to randomisation Units: Months			
median	2.02	2.14	

inter-quartile range (Q1-Q3)	1.22 to 3.12	1.31 to 3.06	-

End points

End points reporting groups

Reporting group title	Chemotherapy alone

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG:

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Reporting group title	Chemotherapy and Cetuximab

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG, and Cetuximab (see Cetuximab dosage and administration details section):

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Primary: Progression-Free Survival (primary endpoint, at interim analysis)

End point title	Progression-Free Survival (primary endpoint, at interim analysis)

End point description:

End point type	Primary

End point timeframe:

Median Progression-Free Survival, associated unadjusted Hazard Ratio (pre-specified primary endpoint) and adjusted HR (secondary) assessed when on 01Nov12 median follow-up was 21.1 months in the chemo alone arm and 19.8 months in the chemo+cetuximab arm

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[1]	119[2]		
Units: Months				
number (confidence interval 95%)	20.5 (16.8 to 26.7)	14.1 (11.8 to 15.9)		

Notes:

[1] - 11 not reached/withdrew consent before/not assessed for RECIST assessment at time of analysis

[2] - 10 not reached/withdrew consent before/not assessed for RECIST assessment at time of analysis

Attachments (see zip file)	KM PFS by Arm (at Interim)/Fig2A.tif

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio
Statistical analysis description: Reference category for hazard ratio: Arm A (Chemotherapy Alone)	
Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	2.12

Statistical analysis title	Adjusted Hazard Ratio
Statistical analysis description: Hazard Ratio adjusted for minimisation factors. Reference category for hazard ratio: Arm A (Chemotherapy Alone)	
Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.059
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	2.04

Primary: Progression Free Survival (at final analysis)

End point title	Progression Free Survival (at final analysis)

End point description:

End point type	Primary

End point timeframe:

Median PFS, unadjusted Hazard Ratio (primary), and Hazard Ratio adjusted for minimisation factors (secondary) assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	129		
Units: Months				
number (confidence interval 95%)	22.0 (18.3 to 26.8)	16.0 (13.8 to 19.0)		

Attachments (see zip file)	KM PFS by Arm (at Final)/F2_KM_PFS_PRIMARY.jpg

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy and Cetuximab v Chemotherapy alone
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.304
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.56

Statistical analysis title	Adjusted Hazard Ratio

Statistical analysis description:

Hazard Ratio adjusted for minimisation factors. Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.401
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.52

Secondary: Overall Survival (at interim analysis)

End point title	Overall Survival (at interim analysis)

End point description:

End point type	Secondary

End point timeframe:

Median Overall Survival and associated unadjusted Hazard Ratio assessed on 1 Nov 2012 when median follow-up was 21.1 months in the chemotherapy alone arm and 19.8 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117[3]	119[4]		
Units: Months				
number (confidence interval 95%)	0 (0 to 0)	39.1 (23.6 to 100)		

Notes:

[3] - 11 not reached/withdrew/not assessed at time of analysis. Median Overall Survival not reached.

[4] - 10 not reached/withdrew/not assessed at time of analysis. Median OS upper CI not reached.

Attachments (see zip file)	KM OS by Arm (at Interim)/Fig2B.tif

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	2.6

Secondary: Overall Survival (at final analysis)

End point title	Overall Survival (at final analysis)

End point description:

End point type	Secondary

End point timeframe:

Median Overall Survival, unadjusted Hazard Ratio, and Hazard Ratio adjusted for minimisation factors assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128[5]	129		
Units: Months				
number (confidence interval 95%)	81.0 (59.6 to 100)	55.0 (43.5 to 71.5)		

Notes:

[5] - (Median Overall Survival Upper CI not reached)

Attachments (see zip file)	KM OS by Arm (at Final)/F7_KM_OS_PRIMARY.jpg

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.036
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	2.05

Statistical analysis title	Adjusted Hazard Ratio

Statistical analysis description:

Hazard Ratio adjusted for minimisation factors. Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	257
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.44
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	2.05

Secondary: Progression Free Survival (pts not on CAPOX, at final analysis)

End point title	Progression Free Survival (pts not on CAPOX, at final analysis)

End point description:

End point type	Secondary

End point timeframe:

Median PFS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[6]	105[7]		
Units: Months				
number (confidence interval 95%)	22.2 (18.3 to 26.8)	15.2 (13.0 to 19.0)		

Notes:

[6] - Excluding patients on CAPOX.

[7] - Excluding patients on CAPOX.

Attachments (see zip file)	KM PFS by Arm (pts not on CAPOX at Final)

Statistical analyses

No statistical analyses for this end point

Secondary: Pathological Resection status (at final analysis)

End point title	Pathological Resection status (at final analysis)

End point description:

End point type	Secondary

End point timeframe:

at final analysis

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	108[8]	100[9]		
Units: subjects				
R0	89	79		
R1	13	17		
R2	6	4		

Notes:

[8] - Only patients who had surgery and resection performed

[9] - Only patients who had surgery and resection performed

Statistical analyses

No statistical analyses for this end point

Secondary: Response to Pre-Operative Chemotherapy (after pre-op, at final analysis)

End point title	Response to Pre-Operative Chemotherapy (after pre-op, at final analysis)

End point description:

End point type	Secondary

End point timeframe:

at final analysis

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120[10]	126[11]		
Units: number				
Complete Response	6	8		
Partial Response	72	85		
Stable Disease	33	23		
Progressive Disease	9	10		

Notes:

[10] - Excludes pts where not assessable or that died/withdrew before pre-operation visit at week 13

[11] - Excludes pts where not assessable or that died/withdrew before pre-operation visit at week 13

Statistical analyses

No statistical analyses for this end point

Secondary: Relative reduction in sum of the largest diameters of lesions on imaging (at final analysis)

End point title	Relative reduction in sum of the largest diameters of lesions on imaging (at final analysis)

End point description:

Relative reduction in the sum of the largest diameters of lesions on imaging from baseline to pre-op visit (i.e. visit closest to, but before, surgery).

End point type	Secondary

End point timeframe:

at final analysis

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	129		
Units: percent				
median (inter-quartile range (Q1-Q3))	33.7 (23.4 to 50.4)	52.2 (16.7 to 72.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical Complications (at final analysis)

End point title	Surgical Complications (at final analysis)

End point description:

End point type	Secondary

End point timeframe:

Surgical complications within 30 days of surgery. Assessed at final analysis.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	113[12]	108[13]		
Units: Number of patients				
At least one surgical complication	28	26		
Deaths during surgery	0	0		
Post-op death (30 days after liver resection)	0	1		

Notes:

[12] - Includes only analysis population who were operated on (prior to disease progression)

[13] - Includes only analysis population who were operated on (prior to disease progression)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Survival (pts on OxMdG, at final analysis)

End point title	Overall Survival (pts on OxMdG, at final analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

Median Overall Survival and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[14]	89[15]		
Units: Months				
number (confidence interval 95%)	59.2 (59.2 to 100)	56.5 (43.5 to 100)		

Notes:

[14] - Excludes patients not on OxMdG.
Median and Upper CI not reached.

[15] - Excludes patients not on OxMdG.
Upper CI not reached.

Attachments (see zip file)	KM OS by Arm (pts on OxMdG at Final)/APP_F1A_OS_KM_OX.

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:	
Reference category for Hazard Ratio: Arm A (Chemotherapy alone)	
Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	2.36

Other pre-specified: Progression Free Survival (pts on OxMdG, at final analysis)

End point title	Progression Free Survival (pts on OxMdG, at final analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

Median PFS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87[16]	89[17]		
Units: Months				
number (confidence interval 95%)	22.2 (18.7 to 26.8)	15.2 (12.6 to 26.6)		

Notes:

[16] - Excludes patients not on OxMdG.

[17] - Excludes patients not on OxMdG.

Attachments (see zip file)	KM PFS by Arm (pts on OxMdG at Final)/APP_F1B_PFS_KM_OX.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Overall Survival (pts who responded to systemic treatment, at final analysis)

End point title	Overall Survival (pts who responded to systemic treatment, at final analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

Median Overall Survival and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[18]	93[19]		
Units: Months				
number (confidence interval 95%)	81.1 (65.7 to 100)	60.7 (48.0 to 100)		

Notes:

[18] - Excluding those who did not respond to systemic treatment.
Upper CI not reached so set to 100
[19] - Excluding those who did not respond to systemic treatment.
Upper CI not reached so set to 100

Attachments (see zip file)	KM OS by Arm (pts responded to sys trt at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.133
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	2.21

Other pre-specified: Progression Free Survival (pts who responded to systemic treatment, at final analysis)

End point title	Progression Free Survival (pts who responded to systemic treatment, at final analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

Median PFS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	78[20]	93[21]		
Units: Months				
number (confidence interval 95%)	23.2 (19.1 to 35.5)	17.6 (14.8 to 27.4)		

Notes:

[20] - Excluding those who did not respond to systemic treatment.

[21] - Excluding those who did not respond to systemic treatment.

Attachments (see zip file)	KM PFS by Arm (pts responded to sys trt at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio
Statistical analysis description:	
Reference category for Hazard Ratio: Arm A (Chemotherapy alone)	
Comparison groups	Chemotherapy and Cetuximab v Chemotherapy alone
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.802
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.51

Other pre-specified: Overall Survival (pts not on CAPOX, at final analysis)

End point title	Overall Survival (pts not on CAPOX, at final analysis)

End point description:

End point type	Other pre-specified

End point timeframe:

Median Overall Survival and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	101[22]	105[23]		
Units: Months				
number (confidence interval 95%)	24.0 (24.0 to 100)	16.1 (13.9 to 100)		

Notes:

[22] - Excluding patients on CAPOX.
Median and upper CI not reached.

[23] - Excluding patients on CAPOX.
Upper CI not reached.

Attachments (see zip file)	KM OS by Arm (pts not on CAPOX at Final)

Statistical analyses

No statistical analyses for this end point

Post-hoc: Overall Survival (pts with left sided tumour, at final analysis)

End point title	Overall Survival (pts with left sided tumour, at final analysis)

End point description:

End point type	Post-hoc

End point timeframe:

Median Overall Survival and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[24]	100[25]		
Units: Months				
number (confidence interval 95%)	81.0 (59.6 to 100)	60.7 (45.8 to 100)		

Notes:

[24] - Excluding patients without left sided tumour.
Upper CI not reached

[25] - Excluding patients without left sided tumour.
Upper CI not reached

Attachments (see zip file)	KM OS by Arm (pts with left tumour at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.148
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.99

Post-hoc: Progression free Survival (pts with left sided tumour, at final analysis)

End point title	Progression free Survival (pts with left sided tumour, at final analysis)

End point description:

End point type	Post-hoc

End point timeframe:

Median PFS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103[26]	100[27]		
Units: Months				
number (confidence interval 95%)	21.9 (16.9 to 26.7)	15.7 (13.8 to 24.3)		

Notes:

[26] - Excluding patients without left sided tumour.

[27] - Excluding patients without left sided tumour.

Attachments (see zip file)	KM PFS by Arm (pts with left tumour at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.741
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.48

Post-hoc: Overall Survival (pts with right sided tumour, at final analysis)

End point title	Overall Survival (pts with right sided tumour, at final analysis)

End point description:

End point type	Post-hoc

End point timeframe:

Median Overall Survival and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[28]	29[29]		
Units: Months				
number (confidence interval 95%)	36.2 (36.2 to 100)	42.6 (25.9 to 58.6)		

Notes:

[28] - Excluding patients without right sided primary tumour.
Median and Upper CI not reached
[29] - Excluding patients without right sided primary tumour.

Attachments (see zip file)	KM OS by Arm (pts with right tumour at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.114
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	3.67

Post-hoc: Progression Free Survival (pts with right sided tumour, at final analysis)

End point title	Progression Free Survival (pts with right sided tumour, at final analysis)

End point description:

End point type	Post-hoc

End point timeframe:

Median PFS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[30]	29[31]		
Units: Months				
number (confidence interval 95%)	24.1 (11.2 to 100)	14.8 (11.4 to 17.6)		

Notes:

[30] - Excluding patients without right sided primary tumour.
Upper CI not reached

[31] - Excluding patients without right sided primary tumour.

Attachments (see zip file)	KM PFS by Arm (pts with right tumour at Final)

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for Hazard Ratio: Arm A (Chemotherapy alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	3.06

Post-hoc: Post Progression Survival (pts who progressed, at final analysis)

End point title	Post Progression Survival (pts who progressed, at final analysis)

End point description:

Defined as time from progression to death from any cause.

End point type	Post-hoc

End point timeframe:

Median PPS and unadjusted Hazard Ratio assessed on 22 May 2018, when median follow-up was 67 in the chemotherapy alone arm and 65 months in the chemotherapy plus cetuximab arm.

End point values	Chemotherapy alone	Chemotherapy and Cetuximab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82[32]	85[33]		
Units: Months				
number (confidence interval 95%)	33.5 (25.3 to 41.2)	23.5 (16.0 to 31.3)		

Notes:

[32] - Only patients who progressed.

[33] - Only patients who progressed.

Attachments (see zip file)	KM PPS by Arm (pts who progressed at Final)/KM PPS by Arm

Statistical analyses

Statistical analysis title	Unadjusted Hazard Ratio

Statistical analysis description:

Reference category for hazard ratio: Arm A (Chemotherapy Alone)

Comparison groups	Chemotherapy alone v Chemotherapy and Cetuximab

Number of subjects included in analysis	167
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.02
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.07
upper limit	2.24

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Investigators to notify SCTU of all SAEs occurring from the time of randomisation until 30 days after the last protocol treatment administration.

Adverse event reporting additional description:

Due to the way adverse event data was collected in the NEW EPOC trial relatedness was not collected for the majority of adverse events recorded. Therefore, the true number of related AEs could be higher than reported in these figures.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Chemotherapy alone

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG:

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Reporting group title	Chemotherapy and Cetuximab

Reporting group description:

Patients in this arm will receive either OxMdG or IrMdG, and Cetuximab (see Cetuximab dosage and administration details section):

OxMdG: l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h), concurrent administration of Oxaliplatin (85 mg/m2 IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial

or

IrMdG: Irinotecan 180 mg/m2 IV over 30 minutes, l-folinic acid (175 mg flat dose IV over 2 h) or d,l-folinic acid (350 mg flat dose IV over 2 h) plus 5 minute bolus of 5FU (400 mg/m2) followed by a 46 h IV infusion of 5FU 2400 mg/m2 repeated every 2 weeks as used in the FOCUS trial in patients intolerant of Oxaliplatin.

NOTE: Prior to the introduction of IrMdG, patients could receive CAPOX:
Oxaliplatin 130 mg/m2 IV over 2 hours plus capecitabine 1000 mg/m2 bid po days 1-15 (28 doses) repeated 3 weekly

Serious adverse events	Chemotherapy alone	Chemotherapy and Cetuximab	
Total subjects affected by serious adverse events			
subjects affected / exposed	52 / 134 (38.81%)	57 / 137 (41.61%)	
number of deaths (all causes)	60	77	
number of deaths resulting from adverse events	1	4	
Vascular disorders			
thromboembolicevent	Additional description: thromboembolicevent		
subjects affected / exposed	8 / 134 (5.97%)	7 / 137 (5.11%)	
occurrences causally related to treatment / all	5 / 10	4 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
hypotension	Additional description: hypotension		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
phlebitis	Additional description: phlebitis		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheralischemia	Additional description: peripheralischemia		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fatigue	Additional description: fatigue		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypothermia	Additional description: hypothermia		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
non-cardiacchestpain	Additional description: non-cardiacchestpain		

subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
fever	Additional description: fever		
subjects affected / exposed	7 / 134 (5.22%)	3 / 137 (2.19%)	
occurrences causally related to treatment / all	0 / 8	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
chestpain-cardiac	Additional description: chestpain-cardiac		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
edemalimbs	Additional description: edemalimbs		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
infusionsiteextravasation	Additional description: infusionsiteextravasation		
subjects affected / exposed	2 / 134 (1.49%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
allergicreaction	Additional description: allergicreaction		
subjects affected / exposed	1 / 134 (0.75%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
dyspnea	Additional description: dyspnea		
subjects affected / exposed	2 / 134 (1.49%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
respiratoryfailure	Additional description: respiratoryfailure		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

thromboembolicevent	Additional description: thromboembolicevent		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
laryngospasm	Additional description: laryngospasm		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
confusion	Additional description: confusion		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Deranged liver function tests	Additional description: Deranged liver function tests		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
neutrophilcountdecreased	Additional description: neutrophilcountdecreased		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
intestinalstomasitebleeding	Additional description: intestinalstomasitebleeding		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
biliaryanastomoticleak	Additional description: biliaryanastomoticleak		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
injury, poisoningandproceduralcomplications -other,infectedpostopcollection	Additional description: injury,poisoningandproceduralcomplications-other, infectedpostopcollection		

subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
acutecoronarysyndrome	Additional description: acutecoronarysyndrome		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 2	
heartfailure	Additional description: heartfailure		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
myocardialinfarction	Additional description: myocardialinfarction		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chestpain-cardiac	Additional description: chestpain-cardiac		
subjects affected / exposed	2 / 134 (1.49%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrialfibrillation	Additional description: atrialfibrillation		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
supraventriculartachycardia	Additional description: supraventriculartachycardia		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiacarrest	Additional description: cardiacarrest		
subjects affected / exposed	0 / 134 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			

headache	Additional description: headache		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
stroke	Additional description: stroke		
subjects affected / exposed	0 / 134 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheralneuropathy	Additional description: peripheralneuropathy		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
syncope	Additional description: syncope		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischemiacerebrovascular	Additional description: ischemiacerebrovascular		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
encephalopathy	Additional description: encephalopathy		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
febrileneutropenia	Additional description: febrileneutropenia		
subjects affected / exposed	2 / 134 (1.49%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anemia	Additional description: anemia		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

constipation	Additional description: constipation		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
diarrhea	Additional description: diarrhea		
subjects affected / exposed	9 / 134 (6.72%)	7 / 137 (5.11%)	
occurrences causally related to treatment / all	4 / 10	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
vomiting	Additional description: vomiting		
subjects affected / exposed	7 / 134 (5.22%)	5 / 137 (3.65%)	
occurrences causally related to treatment / all	8 / 13	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
obstructiongastric	Additional description: obstructiongastric		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominalpain	Additional description: abdominalpain		
subjects affected / exposed	5 / 134 (3.73%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	1 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
bowelobstruction	Additional description: bowelobstruction		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
mucositisoral	Additional description: mucositisoral		
subjects affected / exposed	0 / 134 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
nausea	Additional description: nausea		
subjects affected / exposed	2 / 134 (1.49%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
uppergastrointestinalhemorrhage	Additional description: uppergastrointestinalhemorrhage		

subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
hepatichemorrhage	Additional description: hepatichemorrhage		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
portalveinthrombosis	Additional description: portalveinthrombosis		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
acutekidneyinjury	Additional description: acutekidneyinjury		
subjects affected / exposed	1 / 134 (0.75%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
backpain	Additional description: backpain		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
devicerelatedinfection	Additional description: devicerelatedinfection		
subjects affected / exposed	3 / 134 (2.24%)	5 / 137 (3.65%)	
occurrences causally related to treatment / all	0 / 3	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
infection	Additional description: infection		
subjects affected / exposed	2 / 134 (1.49%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
anorectalinfection	Additional description: anorectalinfection		

subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
infectionsandinfestations-other, infectionunknownactiology	Additional description: infectionsandinfestations-other, infectionunknownactiology		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
abdominalinfection	Additional description: abdominalinfection		
subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis	Additional description: sepsis		
subjects affected / exposed	2 / 134 (1.49%)	5 / 137 (3.65%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
lunginfection	Additional description: lunginfection		
subjects affected / exposed	2 / 134 (1.49%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
biliarytractinfection	Additional description: biliarytractinfection		
subjects affected / exposed	0 / 134 (0.00%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
hypomagnesemia	Additional description: hypomagnesemia		
subjects affected / exposed	0 / 134 (0.00%)	1 / 137 (0.73%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dehydration	Additional description: dehydration		
subjects affected / exposed	5 / 134 (3.73%)	2 / 137 (1.46%)	
occurrences causally related to treatment / all	2 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
hyperglycemia	Additional description: hyperglycemia		

subjects affected / exposed	1 / 134 (0.75%)	0 / 137 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Chemotherapy alone	Chemotherapy and Cetuximab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 134 (98.51%)	136 / 137 (99.27%)	
Vascular disorders			
phlebitis	Additional description: phlebitis		
subjects affected / exposed	20 / 134 (14.93%)	18 / 137 (13.14%)	
occurrences (all)	45	23	
thromboembolicevent	Additional description: thromboembolicevent		
subjects affected / exposed	9 / 134 (6.72%)	10 / 137 (7.30%)	
occurrences (all)	11	14	
General disorders and administration site conditions			
flulikesymptoms	Additional description: flulikesymptoms		
subjects affected / exposed	3 / 134 (2.24%)	8 / 137 (5.84%)	
occurrences (all)	4	8	
fever	Additional description: fever		
subjects affected / exposed	7 / 134 (5.22%)	6 / 137 (4.38%)	
occurrences (all)	7	7	
fatigue	Additional description: fatigue		
subjects affected / exposed	10 / 134 (7.46%)	3 / 137 (2.19%)	
occurrences (all)	27	5	
Respiratory, thoracic and mediastinal disorders			
sorethroat	Additional description: sorethroat		
subjects affected / exposed	3 / 134 (2.24%)	7 / 137 (5.11%)	
occurrences (all)	3	10	
hiccups	Additional description: hiccups		
subjects affected / exposed	6 / 134 (4.48%)	8 / 137 (5.84%)	
occurrences (all)	11	9	
epistaxis	Additional description: epistaxis		

subjects affected / exposed	16 / 134 (11.94%)	12 / 137 (8.76%)	
occurrences (all)	24	20	
cough	Additional description: cough		
subjects affected / exposed	8 / 134 (5.97%)	10 / 137 (7.30%)	
occurrences (all)	10	12	
dyspnea	Additional description: dyspnea		
subjects affected / exposed	9 / 134 (6.72%)	12 / 137 (8.76%)	
occurrences (all)	14	17	
Psychiatric disorders			
anxiety	Additional description: anxiety		
subjects affected / exposed	8 / 134 (5.97%)	4 / 137 (2.92%)	
occurrences (all)	13	5	
insomnia	Additional description: insomnia		
subjects affected / exposed	17 / 134 (12.69%)	13 / 137 (9.49%)	
occurrences (all)	47	41	
depression	Additional description: depression		
subjects affected / exposed	12 / 134 (8.96%)	14 / 137 (10.22%)	
occurrences (all)	24	23	
Investigations			
neutrophilcountdecreased	Additional description: neutrophilcountdecreased		
subjects affected / exposed	72 / 134 (53.73%)	64 / 137 (46.72%)	
occurrences (all)	194	152	
Deranged liver function tests	Additional description: Deranged liver function tests		
subjects affected / exposed	18 / 134 (13.43%)	14 / 137 (10.22%)	
occurrences (all)	91	110	
Nervous system disorders			
dysgeusia	Additional description: dysgeusia		
subjects affected / exposed	30 / 134 (22.39%)	23 / 137 (16.79%)	
occurrences (all)	62	57	
headache	Additional description: headache		
subjects affected / exposed	8 / 134 (5.97%)	10 / 137 (7.30%)	
occurrences (all)	12	15	
dizziness	Additional description: dizziness		
subjects affected / exposed	16 / 134 (11.94%)	8 / 137 (5.84%)	
occurrences (all)	23	15	
lethargy	Additional description: lethargy		

subjects affected / exposed	111 / 134 (82.84%)	124 / 137 (90.51%)	
occurrences (all)	718	718	
peripheralneuropathy	Additional description: peripheralneuropathy		
subjects affected / exposed	120 / 134 (89.55%)	112 / 137 (81.75%)	
occurrences (all)	806	707	
Blood and lymphatic system disorders			
other-platelets	Additional description: other-platelets		
subjects affected / exposed	75 / 134 (55.97%)	55 / 137 (40.15%)	
occurrences (all)	293	192	
other-whitecellcountlow	Additional description: other-whitecellcountlow		
subjects affected / exposed	48 / 134 (35.82%)	55 / 137 (40.15%)	
occurrences (all)	145	137	
anemia	Additional description: anemia		
subjects affected / exposed	78 / 134 (58.21%)	83 / 137 (60.58%)	
occurrences (all)	468	417	
Eye disorders			
wateringeyes	Additional description: wateringeyes		
subjects affected / exposed	8 / 134 (5.97%)	4 / 137 (2.92%)	
occurrences (all)	10	9	
Gastrointestinal disorders			
flatulence	Additional description: flatulence		
subjects affected / exposed	8 / 134 (5.97%)	7 / 137 (5.11%)	
occurrences (all)	11	13	
vomiting	Additional description: vomiting		
subjects affected / exposed	46 / 134 (34.33%)	38 / 137 (27.74%)	
occurrences (all)	75	64	
abdominalpain	Additional description: abdominalpain		
subjects affected / exposed	12 / 134 (8.96%)	9 / 137 (6.57%)	
occurrences (all)	20	11	
gastroesophagealrefluxdisease/dyspepsia	Additional description: gastroesophagealrefluxdisease/dyspepsia		
subjects affected / exposed	25 / 134 (18.66%)	32 / 137 (23.36%)	
occurrences (all)	45	63	
diarrhea	Additional description: diarrhea		
subjects affected / exposed	95 / 134 (70.90%)	98 / 137 (71.53%)	
occurrences (all)	368	385	
mucositisoral	Additional description: mucositisoral		

subjects affected / exposed	69 / 134 (51.49%)	101 / 137 (73.72%)	
occurrences (all)	203	448	
nausea	Additional description: nausea		
subjects affected / exposed	92 / 134 (68.66%)	81 / 137 (59.12%)	
occurrences (all)	343	256	
drymouth	Additional description: drymouth		
subjects affected / exposed	11 / 134 (8.21%)	11 / 137 (8.03%)	
occurrences (all)	21	25	
constipation	Additional description: constipation		
subjects affected / exposed	47 / 134 (35.07%)	55 / 137 (40.15%)	
occurrences (all)	131	170	
Skin and subcutaneous tissue disorders			
nailchanges	Additional description: nailchanges		
subjects affected / exposed	24 / 134 (17.91%)	47 / 137 (34.31%)	
occurrences (all)	45	121	
alopecia	Additional description: alopecia		
subjects affected / exposed	38 / 134 (28.36%)	37 / 137 (27.01%)	
occurrences (all)	119	92	
palmar-plantarerythrodysesthesiasyndrome	Additional description: palmar-plantarerythrodysesthesiasyndrome		
subjects affected / exposed	41 / 134 (30.60%)	86 / 137 (62.77%)	
occurrences (all)	86	270	
dryskin	Additional description: dryskin		
subjects affected / exposed	9 / 134 (6.72%)	16 / 137 (11.68%)	
occurrences (all)	22	29	
skinrash	Additional description: skinrash		
subjects affected / exposed	43 / 134 (32.09%)	125 / 137 (91.24%)	
occurrences (all)	76	811	
pruritus	Additional description: pruritus		
subjects affected / exposed	4 / 134 (2.99%)	7 / 137 (5.11%)	
occurrences (all)	12	10	
Musculoskeletal and connective tissue disorders			
pain	Additional description: pain		
subjects affected / exposed	84 / 134 (62.69%)	84 / 137 (61.31%)	
occurrences (all)	298	250	
myalgia	Additional description: myalgia		

subjects affected / exposed	2 / 134 (1.49%)	7 / 137 (5.11%)	
occurrences (all)	2	11	
Infections and infestations			
upperrespiratorytractinfection	Additional description: upperrespiratorytractinfection		
subjects affected / exposed	13 / 134 (9.70%)	9 / 137 (6.57%)	
occurrences (all)	17	12	
devicerelatedinfection	Additional description: devicerelatedinfection		
subjects affected / exposed	9 / 134 (6.72%)	9 / 137 (6.57%)	
occurrences (all)	10	12	
lunginfection	Additional description: lunginfection		
subjects affected / exposed	5 / 134 (3.73%)	10 / 137 (7.30%)	
occurrences (all)	7	11	
thrush	Additional description: thrush		
subjects affected / exposed	10 / 134 (7.46%)	9 / 137 (6.57%)	
occurrences (all)	30	15	
skininfection	Additional description: skininfection		
subjects affected / exposed	1 / 134 (0.75%)	7 / 137 (5.11%)	
occurrences (all)	1	9	
Metabolism and nutrition disorders			
hypokalaemia	Additional description: hypokalaemia		
subjects affected / exposed	8 / 134 (5.97%)	8 / 137 (5.84%)	
occurrences (all)	16	11	
anorexia	Additional description: anorexia		
subjects affected / exposed	56 / 134 (41.79%)	61 / 137 (44.53%)	
occurrences (all)	159	123	
hypomagnesemia	Additional description: hypomagnesemia		
subjects affected / exposed	19 / 134 (14.18%)	29 / 137 (21.17%)	
occurrences (all)	59	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2007	- Urgent safety measure reduce dose of capecitabine - Approving GPv3 18th Oct 07
16 January 2008	Clarification of treatment regimens, Tissue collection details. Stratification details.
14 March 2008	Changing formulation of cetuximab from 2mg/ml to 5mg/ml + other minor amendments
04 July 2008	Urgent safety measure to introduce KRAS genotyping
11 July 2008	Wrong date for PIS on consent form for KRAS
16 September 2008	- Addition of irinotecan docs updated - Updated investigator brochure
22 April 2009	- Clarification of randomisation stratification criteria - QoL Questionnaire v4 minor amendement - Update of kRAS PIS & ICF
28 July 2010	Removal of CAPOX chemotherapy regimen
08 December 2010	Update to cetuximab infusion rate, update to radiation risk assess. Addition 5 sites. Update to delivery of chemo following cetuximab. Change to kRAS ICF.
16 January 2012	Update to sample size. Study size now 288 patients. Change to PIS to reflect this. Removal of Mount Vernon, and Basildon
23 November 2012	Patient Information Letter – subsequent to cessation of cetuximab and recruitment to study
02 January 2013	Kras – seeking consent from 22 patients who entered study prior to implementing Kras consent
08 February 2013	Informing MHRA of cessation of cetuximab and recruitment

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

01 November 2012	The study was closed to recruitment by the trial steering committee on advice from the data monitoring and ethics committee on Nov 1, 2012, when the predefined futility criteria were met, using a method proposed by Freidlin and colleagues (the lower limit of the 95% CI for the progression-free survival hazard ratio [HR] was >1, where the reference category for the hazard ratio was Arm A [Chemotherapy alone]).	-

Notes:

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24717919

http://www.ncbi.nlm.nih.gov/pubmed/27434036