



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 |
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Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 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,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

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 | I-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/m ² 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/m ² ; 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/m ² 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/m ² 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: I-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/m ² 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/m ² ; 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/m ² to be administered over 2 hours and thereafter fortnightly infusions, or a loading dose of 400 mg/m ² followed by a weekly infusion of 250 mg/m ² 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 | | | |
| acute coronary syndrome | Additional description: acute coronary syndrome | | |
| 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 | |
| heart failure | Additional description: heart failure | | |
| 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 | |
| myocardial infarction | Additional description: myocardial infarction | | |
| 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 | |
| chest pain-cardiac | Additional description: chest pain-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 | |
| atrial fibrillation | Additional description: atrial fibrillation | | |
| 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 | |
| supraventricular tachycardia | Additional description: supraventricular tachycardia | | |
| 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 | |
| cardiac arrest | Additional description: cardiac arrest | | |
| 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, infectionunknownaetiology | Additional description: infectionsandinfestations-other, infectionunknownaetiology | | |
| 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 occurrences (all) | 2 / 134 (1.49%) 2 | 7 / 137 (5.11%) 11 | |
| Infections and infestations | | | |
| upperrespiratorytractinfection | Additional description: upperrespiratorytractinfection | | |
| subjects affected / exposed occurrences (all) | 13 / 134 (9.70%) 17 | 9 / 137 (6.57%) 12 | |
| devicerelatedinfection | Additional description: devicerelatedinfection | | |
| subjects affected / exposed occurrences (all) | 9 / 134 (6.72%) 10 | 9 / 137 (6.57%) 12 | |
| lunginfection | Additional description: lunginfection | | |
| subjects affected / exposed occurrences (all) | 5 / 134 (3.73%) 7 | 10 / 137 (7.30%) 11 | |
| thrush | Additional description: thrush | | |
| subjects affected / exposed occurrences (all) | 10 / 134 (7.46%) 30 | 9 / 137 (6.57%) 15 | |
| skininfection | Additional description: skininfection | | |
| subjects affected / exposed occurrences (all) | 1 / 134 (0.75%) 1 | 7 / 137 (5.11%) 9 | |
| Metabolism and nutrition disorders | | | |
| hypokalaemia | Additional description: hypokalaemia | | |
| subjects affected / exposed occurrences (all) | 8 / 134 (5.97%) 16 | 8 / 137 (5.84%) 11 | |
| anorexia | Additional description: anorexia | | |
| subjects affected / exposed occurrences (all) | 56 / 134 (41.79%) 159 | 61 / 137 (44.53%) 123 | |
| hypomagnesemia | Additional description: hypomagnesemia | | |
| subjects affected / exposed occurrences (all) | 19 / 134 (14.18%) 59 | 29 / 137 (21.17%) 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 amendment - 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>