



## Clinical trial results: Short Course Oncology Therapy - A study of adjuvant chemotherapy in colorectal cancer

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2007-003957-10 |
| Trial protocol           | GB DK ES SE DE |
| Global end of trial date | 30 April 2019  |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 01 January 2020 |
| First version publication date | 01 January 2020 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | SCOT-2007-01 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |                               |
|------------------------------------|-------------------------------|
| ISRCTN number                      | ISRCTN59757862                |
| ClinicalTrials.gov id (NCT number) | -                             |
| WHO universal trial number (UTN)   | -                             |
| Other trial identifiers            | Sponsor Ref Number: WN07ON160 |

Notes:

### Sponsors

|                              |                                                                                                                                |
|------------------------------|--------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | NHS Greater Glasgow and Clyde                                                                                                  |
| Sponsor organisation address | Clinical Research and Development Central Office, Dykebar Hospital, Ward 11, Grahamston Road, Paisley, United Kingdom, PA2 7DE |
| Public contact               | Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4172, margaret.fegen@ggc.scot.nhs.uk                                |
| Scientific contact           | Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0141 314 4172, margaret.fegen@ggc.scot.nhs.uk                                |
| Sponsor organisation name    | University of Glasgow                                                                                                          |
| Sponsor organisation address | University Avenue, Glasgow, United Kingdom, G12 8QQ                                                                            |
| Public contact               | Dr Debra Stuart, University of Glasgow, 0141 330 4539, debra.stuart@glasgow.ac.uk                                              |
| Scientific contact           | Dr Debra Stuart, University of Glasgow, 0141 330 4539, debra.stuart@glasgow.ac.uk                                              |

Notes:

### Paediatric regulatory details

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

Notes:

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## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 08 August 2017  |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 31 October 2016 |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 30 April 2019   |
| Was the trial ended prematurely?                     | No              |

Notes:

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## General information about the trial

Main objective of the trial:

The study aims to ascertain whether 3 months of treatment for colorectal cancer is as efficacious as 6 months with the further aim of providing robust evidence on the cost effectiveness of reducing the toxicity of adjuvant therapy.

Protection of trial subjects:

Patients on both study arms received standard chemotherapy agents with standard schedules. The difference is in the duration of treatments - 24 weeks on the standard (control) arm and 12 weeks on the experimental arm.

The study therefore posed no risk in terms of increased toxicity for patients as the experimental arm reduced exposure to the chemotherapy.

The difference between the study arms was however monitored annually by an IDMC both in terms of toxicity and efficacy,

Background therapy: -

Evidence for comparator:

Colorectal cancer is the fourth most common cancer worldwide, with 1,360,000 cases occurring annually, and is the fifth most common cause of death from cancer, causing 694000 deaths.(1) Postoperative adjuvant fluoropyrimidine chemotherapy was first shown to improve outcomes for patients with stage III colon cancer by Moertel and colleagues.(2) The addition of oxaliplatin to a fluoropyrimidine chemotherapy backbone produced additional benefit,(3, 4, 5) and oxaliplatin-containing chemotherapy is a recommended adjuvant treatment for stage III colon cancer.(6, 7). The current standard duration of adjuvant chemotherapy for colorectal cancer is 6 months.

1.Ferlay J Soerjomataram I Ervik M et al.

GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC cancer base no. 11.

International Agency for Research on Cancer, Lyon; 2013

2.Moertel CG Fleming TR Macdonald JS et al.

Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma.

N Engl J Med. 1990; 322: 352-358

3.Andre T Boni C Mounedji-Boudiaf L et al.

Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer.

N Engl J Med. 2004; 350: 2343-2351

4.Kuebler JP Wieand HS O'Connell MJ et al.

Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07.

J Clin Oncol. 2007; 25: 2198-2204

5.Haller DG Tabernero J Maroun J et al.

Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer.

J Clin Oncol. 2011; 29: 1465-1471

6.Schmoll HJ Van Cutsem E Stein A et al.

ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making.

Ann Oncol. 2012; 23: 2479-2516

7.National Comprehensive Cancer Network

Colon cancer (version 2.2107).

[http://www.nccn.org/professionals/physician\\_gls/pdf/colon.pdf](http://www.nccn.org/professionals/physician_gls/pdf/colon.pdf)

(accessed June 24, 2017)

|                                                           |                               |
|-----------------------------------------------------------|-------------------------------|
| Actual start date of recruitment                          | 09 May 2008                   |
| Long term follow-up planned                               | Yes                           |
| Long term follow-up rationale                             | Efficacy, Scientific research |
| Long term follow-up duration                              | 10 Years                      |
| Independent data monitoring committee (IDMC) involvement? | Yes                           |

Notes:

### Population of trial subjects

#### Subjects enrolled per country

|                                      |                      |
|--------------------------------------|----------------------|
| Country: Number of subjects enrolled | Australia: 197       |
| Country: Number of subjects enrolled | New Zealand: 16      |
| Country: Number of subjects enrolled | Spain: 237           |
| Country: Number of subjects enrolled | Sweden: 83           |
| Country: Number of subjects enrolled | United Kingdom: 5300 |
| Country: Number of subjects enrolled | Denmark: 311         |
| Worldwide total number of subjects   | 6144                 |
| EEA total number of subjects         | 5931                 |

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)                      | 3340 |
| From 65 to 84 years                       | 2804 |
| 85 years and over                         | 0    |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited from 244 centres in six countries (the UK, Denmark, Spain, Sweden, Australia, and New Zealand) between March 27, 2008, and Nov 29, 2013

### Pre-assignment

Screening details:

For a period in the study some UK centres (selected at random) registered patients onto the study before they started treatment. Patients were then invited to be randomised at 3 months to continue to 6 months of treatment or stop at that point. 215 were recruited via this route of whom 156 were subsequently randomised.

### Period 1

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

Blinding implementation details:

N/A

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | 12 weeks |

Arm description:

12 weeks of adjuvant fluoropyrimidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | 5-FU            |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

5-FU 400mg/m<sup>2</sup> IV bolus followed by 5-FU 2400mg/m<sup>2</sup> IV over 46 hours every 2 weeks

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Oxaliplatin     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

130mg/m<sup>2</sup> IV on 3 weekly cycle or 85mg/m<sup>2</sup> IV on 2 weekly cycle

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

Dosage and administration details:

1000mg/m<sup>2</sup> twice daily for 14 days

|                                        |              |
|----------------------------------------|--------------|
| Investigational medicinal product name | Folinic Acid |
| Investigational medicinal product code |              |
| Other name                             |              |

|                          |                 |
|--------------------------|-----------------|
| Pharmaceutical forms     | Injection       |
| Routes of administration | Intravenous use |

Dosage and administration details:

L-Folinic acid 175 mg or folinic acid 350 mg 2 weekly

|                  |          |
|------------------|----------|
| <b>Arm title</b> | 24 weeks |
|------------------|----------|

Arm description:

24 weeks of adjuvant flouoropyrimidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | 5-FU              |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

5-FU 400mg/m<sup>2</sup> IV bolus followed by 5-FU 2400mg/m<sup>2</sup> IV over 46 hours every 2 weeks

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Oxaliplatin     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

130mg/m<sup>2</sup> IV on 3 weekly cycle or 85mg/m<sup>2</sup> IV on 2 weekly cycle

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

Dosage and administration details:

1000mg/m<sup>2</sup> twice daily for 14 days on 3 weekly cycle

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Folinic Acid    |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Injection       |
| Routes of administration               | Intravenous use |

Dosage and administration details:

L-Folinic acid 175 mg or folinic acid 350 mg 2 weekly

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 12 weeks | 24 weeks |
|-----------------------------------------------------|----------|----------|
| Started                                             | 3044     | 3044     |
| Completed                                           | 3044     | 3044     |

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Notes:

[1] - 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: Some randomly selected centres in the UK recruited patients to the study prior to treatment starting and patients were then invited to be randomised after 3 months of treatment. 215 patients were recruited in this way of whom 159 were randomised. All other patients were randomised prior to treatment starting. Only randomised patients were used in the comparison of the study arms in the baseline period, for efficacy end-points and safety. All patients are reported in worldwide recruitment.

## Baseline characteristics

### Reporting groups

|                                                                                                                                                           |          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Reporting group title                                                                                                                                     | 12 weeks |
| Reporting group description:                                                                                                                              |          |
| 12 weeks of adjuvant flouropyrimidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly |          |
| Reporting group title                                                                                                                                     | 24 weeks |
| Reporting group description:                                                                                                                              |          |
| 24 weeks of adjuvant flouropyrimidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly |          |

| Reporting group values                             | 12 weeks | 24 weeks | Total |
|----------------------------------------------------|----------|----------|-------|
| Number of subjects                                 | 3044     | 3044     | 6088  |
| Age categorical                                    |          |          |       |
| Units: Subjects                                    |          |          |       |
| In utero                                           |          |          | 0     |
| Preterm newborn infants (gestational age < 37 wks) |          |          | 0     |
| Newborns (0-27 days)                               |          |          | 0     |
| Infants and toddlers (28 days-23 months)           |          |          | 0     |
| Children (2-11 years)                              |          |          | 0     |
| Adolescents (12-17 years)                          |          |          | 0     |
| Adults (18-64 years)                               |          |          | 0     |
| From 65-84 years                                   |          |          | 0     |
| 85 years and over                                  |          |          | 0     |
| Age continuous                                     |          |          |       |
| Age at randomisation                               |          |          |       |
| Units: years                                       |          |          |       |
| median                                             | 65       | 65       |       |
| inter-quartile range (Q1-Q3)                       | 58 to 70 | 58 to 70 | -     |
| Gender categorical                                 |          |          |       |
| Units: Subjects                                    |          |          |       |
| Female                                             | 1201     | 1200     | 2401  |
| Male                                               | 1843     | 1844     | 3687  |
| Disease site                                       |          |          |       |
| Units: Subjects                                    |          |          |       |
| Colon                                              | 2492     | 2495     | 4987  |
| Rectum                                             | 552      | 549      | 1101  |
| Performance status at randomisation                |          |          |       |
| Units: Subjects                                    |          |          |       |
| ECOG - 0                                           | 2190     | 2144     | 4334  |
| ECOG - 1                                           | 854      | 900      | 1754  |
| T-Stage                                            |          |          |       |
| Units: Subjects                                    |          |          |       |
| T0                                                 | 1        | 3        | 4     |
| T1                                                 | 92       | 95       | 187   |
| T2                                                 | 284      | 283      | 567   |
| T3                                                 | 1749     | 1748     | 3497  |

|                                                                                                                  |                                 |                                 |                                   |
|------------------------------------------------------------------------------------------------------------------|---------------------------------|---------------------------------|-----------------------------------|
| T4<br>TX                                                                                                         | 917<br>1                        | 915<br>0                        | 1832<br>1                         |
| N-Stage<br>Units: Subjects                                                                                       |                                 |                                 |                                   |
| N0<br>N1<br>N2                                                                                                   | 559<br>1731<br>754              | 557<br>1732<br>755              | 1116<br>3463<br>1509              |
| Planned treatment<br>Units: Subjects                                                                             |                                 |                                 |                                   |
| FOLFOX<br>CAPOX                                                                                                  | 993<br>2051                     | 988<br>2056                     | 1981<br>4107                      |
| Starting dose of capecitabine (if CAPOX<br>planned)<br>Units: Subjects                                           |                                 |                                 |                                   |
| 750mg/m2<br>800mg/m2<br>1000mg/m2<br>NA - FOLFOX<br>Not recorded                                                 | 348<br>72<br>1369<br>993<br>262 | 349<br>78<br>1370<br>988<br>259 | 697<br>150<br>2739<br>1981<br>521 |
| High risk stage II<br>Units: Subjects                                                                            |                                 |                                 |                                   |
| Yes<br>No                                                                                                        | 551<br>2493                     | 545<br>2499                     | 1096<br>4992                      |
| Randomisation timepoint                                                                                          |                                 |                                 |                                   |
| Initially a proportion of patients were randomised at 12 weeks either to stop or continue for a further 12 weeks |                                 |                                 |                                   |
| Units: Subjects                                                                                                  |                                 |                                 |                                   |
| 12 weeks<br>Baseline                                                                                             | 80<br>2964                      | 79<br>2965                      | 159<br>5929                       |

## End points

### End points reporting groups

|                                                                                                                                                                                         |          |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|
| Reporting group title                                                                                                                                                                   | 12 weeks |
| Reporting group description:<br>12 weeks of adjuvant flouropymidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly |          |
| Reporting group title                                                                                                                                                                   | 24 weeks |
| Reporting group description:<br>24 weeks of adjuvant flouropymidine treatment - either receiving OxMdG (Oxaliplatin and 5-FU) 2 weekly or Xelox (Oxaliplatin and Capecitabine) 3 weekly |          |

### Primary: Disease free survival

|                                                                                                                                                                                                                            |                       |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| End point title                                                                                                                                                                                                            | Disease free survival |
| End point description:                                                                                                                                                                                                     |                       |
| End point type                                                                                                                                                                                                             | Primary               |
| End point timeframe:<br>Disease free survival is defined as the time from randomisation (or trial registration for those randomised after 3 months of therapy) to relapse, development of new colorectal primary or death. |                       |

| End point values                          | 12 weeks            | 24 weeks            |  |  |
|-------------------------------------------|---------------------|---------------------|--|--|
| Subject group type                        | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed               | 3044                | 3044                |  |  |
| Units: Percentage disease free at 3 years |                     |                     |  |  |
| number (confidence interval 95%)          | 76.7 (75.1 to 78.2) | 77.1 (75.6 to 78.6) |  |  |

### Statistical analyses

|                                                                          |                        |
|--------------------------------------------------------------------------|------------------------|
| Statistical analysis title                                               | Cox regression         |
| Statistical analysis description:<br>Comparison of disease-free survival |                        |
| Comparison groups                                                        | 12 weeks v 24 weeks    |
| Number of subjects included in analysis                                  | 6088                   |
| Analysis specification                                                   | Pre-specified          |
| Analysis type                                                            | non-inferiority        |
| P-value                                                                  | = 0.012 <sup>[1]</sup> |
| Method                                                                   | Regression, Cox        |
| Parameter estimate                                                       | Hazard ratio (HR)      |
| Point estimate                                                           | 1.006                  |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.909   |
| upper limit         | 1.114   |

Notes:

[1] - 1-sided non-inferiority p-value from Cox model including terms for study arm and minimisation factors.

## Secondary: Overall survival

|                                                     |                  |
|-----------------------------------------------------|------------------|
| End point title                                     | Overall survival |
| End point description:                              |                  |
| End point type                                      | Secondary        |
| End point timeframe:                                |                  |
| Patients were followed up for a maximum of 8 years. |                  |

| End point values                 | 12 weeks            | 24 weeks            |  |  |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type               | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed      | 3044                | 3044                |  |  |
| Units: Percent alive at 3 years  |                     |                     |  |  |
| number (confidence interval 95%) | 90.0 (88.9 to 91.1) | 89.6 (88.5 to 90.7) |  |  |

## Statistical analyses

|                                                                                                                      |                        |
|----------------------------------------------------------------------------------------------------------------------|------------------------|
| Statistical analysis title                                                                                           | Cox regression         |
| Statistical analysis description:                                                                                    |                        |
| OS was compared between the study arms using a Cox model incorporating terms for study arm and minimisation factors. |                        |
| Comparison groups                                                                                                    | 12 weeks v 24 weeks    |
| Number of subjects included in analysis                                                                              | 6088                   |
| Analysis specification                                                                                               | Pre-specified          |
| Analysis type                                                                                                        | non-inferiority        |
| P-value                                                                                                              | = 0.035 <sup>[2]</sup> |
| Method                                                                                                               | Regression, Cox        |
| Parameter estimate                                                                                                   | Hazard ratio (HR)      |
| Point estimate                                                                                                       | 0.994                  |
| Confidence interval                                                                                                  |                        |
| level                                                                                                                | 95 %                   |
| sides                                                                                                                | 2-sided                |
| lower limit                                                                                                          | 0.964                  |
| upper limit                                                                                                          | 1.143                  |

Notes:

[2] - 1-sided test for non-inferiority for overall survival.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events systematically collected in the first 868 patients

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |            |
|-----------------|------------|
| Dictionary name | NCI CTC AE |
|-----------------|------------|

|                    |   |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

### Reporting groups

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Patients with CTC AE assessment on 3 month arm |
|-----------------------|------------------------------------------------|

Reporting group description:

In the first 868 patients CTC AE data was systematically assessed; 434 on each arm.

|                       |                                                |
|-----------------------|------------------------------------------------|
| Reporting group title | Patients with CTC AE assessment on 6 month arm |
|-----------------------|------------------------------------------------|

Reporting group description:

In the first 868 patients CTC AE data was systematically assessed; 434 on each arm.

| <b>Serious adverse events</b>                     | Patients with CTC AE assessment on 3 month arm | Patients with CTC AE assessment on 6 month arm |  |
|---------------------------------------------------|------------------------------------------------|------------------------------------------------|--|
| Total subjects affected by serious adverse events |                                                |                                                |  |
| subjects affected / exposed                       | 88 / 434 (20.28%)                              | 121 / 434 (27.88%)                             |  |
| number of deaths (all causes)                     | 87                                             | 84                                             |  |
| number of deaths resulting from adverse events    | 2                                              | 3                                              |  |
| Nervous system disorders                          |                                                |                                                |  |
| Neuropathy - sensory                              |                                                |                                                |  |
| subjects affected / exposed                       | 4 / 434 (0.92%)                                | 5 / 434 (1.15%)                                |  |
| occurrences causally related to treatment / all   | 4 / 4                                          | 5 / 5                                          |  |
| deaths causally related to treatment / all        | 0 / 0                                          | 0 / 0                                          |  |
| Blood and lymphatic system disorders              |                                                |                                                |  |
| Anaemia                                           |                                                |                                                |  |
| subjects affected / exposed                       | 2 / 434 (0.46%)                                | 2 / 434 (0.46%)                                |  |
| occurrences causally related to treatment / all   | 2 / 2                                          | 2 / 2                                          |  |
| deaths causally related to treatment / all        | 0 / 0                                          | 0 / 0                                          |  |
| Neutropenia                                       |                                                |                                                |  |
| subjects affected / exposed                       | 7 / 434 (1.61%)                                | 10 / 434 (2.30%)                               |  |
| occurrences causally related to treatment / all   | 7 / 7                                          | 10 / 10                                        |  |
| deaths causally related to treatment / all        | 0 / 0                                          | 1 / 1                                          |  |
| Thrombocytopenia                                  |                                                |                                                |  |

|                                                      |                  |                  |  |
|------------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                          | 0 / 434 (0.00%)  | 2 / 434 (0.46%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 2 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 1 / 1            |  |
| General disorders and administration site conditions |                  |                  |  |
| Fatigue                                              |                  |                  |  |
| subjects affected / exposed                          | 11 / 434 (2.53%) | 6 / 434 (1.38%)  |  |
| occurrences causally related to treatment / all      | 12 / 12          | 6 / 6            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pain - Other (specify)                               |                  |                  |  |
| subjects affected / exposed                          | 8 / 434 (1.84%)  | 16 / 434 (3.69%) |  |
| occurrences causally related to treatment / all      | 8 / 8            | 16 / 16          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pain - Select                                        |                  |                  |  |
| subjects affected / exposed                          | 8 / 434 (1.84%)  | 10 / 434 (2.30%) |  |
| occurrences causally related to treatment / all      | 8 / 8            | 12 / 12          |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                           |                  |                  |  |
| Constipation                                         |                  |                  |  |
| subjects affected / exposed                          | 1 / 434 (0.23%)  | 2 / 434 (0.46%)  |  |
| occurrences causally related to treatment / all      | 1 / 1            | 2 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Anorexia                                             |                  |                  |  |
| subjects affected / exposed                          | 3 / 434 (0.69%)  | 2 / 434 (0.46%)  |  |
| occurrences causally related to treatment / all      | 3 / 3            | 2 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                            |                  |                  |  |
| subjects affected / exposed                          | 32 / 434 (7.37%) | 32 / 434 (7.37%) |  |
| occurrences causally related to treatment / all      | 36 / 36          | 34 / 34          |  |
| deaths causally related to treatment / all           | 0 / 0            | 1 / 1            |  |
| Mucositis (clinical exam)                            |                  |                  |  |
| subjects affected / exposed                          | 0 / 434 (0.00%)  | 3 / 434 (0.69%)  |  |
| occurrences causally related to treatment / all      | 0 / 0            | 3 / 3            |  |
| deaths causally related to treatment / all           | 0 / 0            | 1 / 1            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Mucositis (functional/symptomatic)              |                  |                  |  |
| subjects affected / exposed                     | 1 / 434 (0.23%)  | 2 / 434 (0.46%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1            |  |
| Nausea                                          |                  |                  |  |
| subjects affected / exposed                     | 15 / 434 (3.46%) | 7 / 434 (1.61%)  |  |
| occurrences causally related to treatment / all | 16 / 16          | 7 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Taste alteration                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 434 (0.23%)  | 1 / 434 (0.23%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vomiting                                        |                  |                  |  |
| subjects affected / exposed                     | 22 / 434 (5.07%) | 14 / 434 (3.23%) |  |
| occurrences causally related to treatment / all | 24 / 24          | 15 / 15          |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Hand-foot syndrome                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 434 (0.23%)  | 0 / 434 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rash                                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 434 (0.23%)  | 1 / 434 (0.23%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| Infection-other (specify)                       |                  |                  |  |
| subjects affected / exposed                     | 6 / 434 (1.38%)  | 6 / 434 (1.38%)  |  |
| occurrences causally related to treatment / all | 7 / 7            | 6 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                                                                                                                                                                                                                                                                                                                     | Patients with CTC AE<br>assessment on 3<br>month arm                                                                   | Patients with CTC AE<br>assessment on 6<br>month arm                                                                     |  |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|--|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                                                                                                                                                                                                                                                               | 420 / 434 (96.77%)                                                                                                     | 425 / 434 (97.93%)                                                                                                       |  |
| Nervous system disorders<br>neuropathy-sensory<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                    | 386 / 434 (88.94%)<br>1297                                                                                             | 402 / 434 (92.63%)<br>2480                                                                                               |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Thrombocytopenia<br>subjects affected / exposed<br>occurrences (all)                                                                                                | 148 / 434 (34.10%)<br>419<br><br>125 / 434 (28.80%)<br>235<br><br>124 / 434 (28.57%)<br>252                            | 203 / 434 (46.77%)<br>894<br><br>192 / 434 (44.24%)<br>493<br><br>157 / 434 (36.18%)<br>499                              |  |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Insomnia<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain - Other (specify)<br>subjects affected / exposed<br>occurrences (all)<br><br>Pain - Select<br>subjects affected / exposed<br>occurrences (all) | 358 / 434 (82.49%)<br>1107<br><br>19 / 434 (4.38%)<br>28<br><br>66 / 434 (15.21%)<br>114<br><br>39 / 434 (8.99%)<br>58 | 385 / 434 (88.71%)<br>2012<br><br>27 / 434 (6.22%)<br>56<br><br>77 / 434 (17.74%)<br>174<br><br>57 / 434 (13.13%)<br>155 |  |
| Eye disorders<br>Photophobia<br>subjects affected / exposed<br>occurrences (all)<br><br>Watery eye                                                                                                                                                                                                                                                    | 11 / 434 (2.53%)<br>21                                                                                                 | 26 / 434 (5.99%)<br>51                                                                                                   |  |

|                                                  |                                                      |                           |  |
|--------------------------------------------------|------------------------------------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 71 / 434 (16.36%)<br>118                             | 100 / 434 (23.04%)<br>333 |  |
| Gastrointestinal disorders                       |                                                      |                           |  |
| Constipation                                     |                                                      |                           |  |
| subjects affected / exposed                      | 127 / 434 (29.26%)                                   | 150 / 434 (34.56%)        |  |
| occurrences (all)                                | 277                                                  | 483                       |  |
| anorexia                                         |                                                      |                           |  |
| subjects affected / exposed                      | 97 / 434 (22.35%)                                    | 153 / 434 (35.25%)        |  |
| occurrences (all)                                | 194                                                  | 346                       |  |
| Diarrhoea                                        |                                                      |                           |  |
| subjects affected / exposed                      | 286 / 434 (65.90%)                                   | 314 / 434 (72.35%)        |  |
| occurrences (all)                                | 720                                                  | 1132                      |  |
| Mucositis (clinical exam)                        |                                                      |                           |  |
| subjects affected / exposed                      | 58 / 434 (13.36%)                                    | 92 / 434 (21.20%)         |  |
| occurrences (all)                                | 106                                                  | 184                       |  |
| Mucositis (functional/symptomatic)               |                                                      |                           |  |
| subjects affected / exposed                      | 131 / 434 (30.18%)                                   | 178 / 434 (41.01%)        |  |
| occurrences (all)                                | 283                                                  | 477                       |  |
| Nausea                                           |                                                      |                           |  |
| subjects affected / exposed                      | 268 / 434 (61.75%)                                   | 299 / 434 (68.89%)        |  |
| occurrences (all)                                | 666                                                  | 936                       |  |
| Taste alteration                                 |                                                      |                           |  |
| subjects affected / exposed                      | 181 / 434 (41.71%)                                   | 235 / 434 (54.15%)        |  |
| occurrences (all)                                | 460                                                  | 869                       |  |
| Vomiting                                         |                                                      |                           |  |
| subjects affected / exposed                      | 104 / 434 (23.96%)                                   | 136 / 434 (31.34%)        |  |
| occurrences (all)                                | 156                                                  | 248                       |  |
| Respiratory, thoracic and mediastinal disorders  |                                                      |                           |  |
| Dyspnoea                                         |                                                      |                           |  |
| subjects affected / exposed                      | 13 / 434 (3.00%)                                     | 23 / 434 (5.30%)          |  |
| occurrences (all)                                | 19                                                   | 40                        |  |
| Skin and subcutaneous tissue disorders           |                                                      |                           |  |
| alopecia                                         |                                                      |                           |  |
| subjects affected / exposed                      | 69 / 434 (15.90%)                                    | 104 / 434 (23.96%)        |  |
| occurrences (all)                                | 141                                                  | 336                       |  |
| Hand and foot syndrome                           | Additional description: Side affect of capecitabiine |                           |  |

|                             |                                                          |                    |  |
|-----------------------------|----------------------------------------------------------|--------------------|--|
| subjects affected / exposed | 138 / 434 (31.80%)                                       | 201 / 434 (46.31%) |  |
| occurrences (all)           | 270                                                      | 619                |  |
| Rash                        |                                                          |                    |  |
| subjects affected / exposed | 53 / 434 (12.21%)                                        | 91 / 434 (20.97%)  |  |
| occurrences (all)           | 88                                                       | 211                |  |
| Infections and infestations |                                                          |                    |  |
| Other - specify             | Additional description: Catch-all fro "other" infections |                    |  |
| subjects affected / exposed | 18 / 434 (4.15%)                                         | 28 / 434 (6.45%)   |  |
| occurrences (all)           | 24                                                       | 41                 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 May 2009      | Amendment Number 4: Protocol amendment to update study objectives, increase the timing from staging of patients to randomisation and subsequent screening investigations, provide clarification around dose banding and body surface area capping, guidance updated for treatment related toxicities, allow use of calcium and magnesium supplements in patients, and numerous administrative changes to provide further clarity around patient and protocol management.                                                                                                                                                                                                                                                                                          |
| 17 July 2009     | Amendment Number 5: Protocol amendment to provide further guidance on allergic reactions to Oxaliplatin and local management of this.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 20 March 2012    | Amendment Number 18: Protocol amendment to discontinue the comparison of the upfront/delayed randomisation of patients, provide clarity around schedule of assessments and timing of investigations, provide further clarity around patient eligibility criteria and timings of screening investigations, allow dose banding of Oxaliplatin, Capecitabine and 5-FU, provide more detailed guidance on the management of toxicity, confirm that patients on Capecitabine should not receive concomitant Warfarin and detail interactions with other known drugs, extend the duration of neurotoxicity questionnaire from 1 year to 2 year follow-up, add a section on the translational research sample collection, and general administrative changes throughout. |
| 20 December 2012 | Amendment Number 22: Protocol amendment to extend the recruitment period of the trial and other general administrative changes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 15 January 2014  | Amendment Number 29: Protocol amendment to clarify details around events which are not required to be reported as SAEs in addition to other general administrative changes to the protocol.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 16 March 2015    | Amendment Number 31: Protocol amendment to update on the final recruitment figures and dates and extend follow-up duration of existing patient in addition to other general administrative changes.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported