



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
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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:

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:

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

(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
Arm title	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/m² IV bolus followed by 5-FU 2400mg/m² 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/m² IV on 3 weekly cycle or 85mg/m² 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/m² 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

Arm title	24 weeks
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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/m² IV bolus followed by 5-FU 2400mg/m² 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/m² IV on 3 weekly cycle or 85mg/m² 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/m² 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

Number of subjects in period 1^[1]	12 weeks	24 weeks
Started	3044	3044
Completed	3044	3044

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	917	915	1832
TX	1	0	1
N-Stage			
Units: Subjects			
N0	559	557	1116
N1	1731	1732	3463
N2	754	755	1509
Planned treatment			
Units: Subjects			
FOLFOX	993	988	1981
CAPOX	2051	2056	4107
Starting dose of capecitabine (if CAPOX planned)			
Units: Subjects			
750mg/m2	348	349	697
800mg/m2	72	78	150
1000mg/m2	1369	1370	2739
NA - FOLFOX	993	988	1981
Not recorded	262	259	521
High risk stage II			
Units: Subjects			
Yes	551	545	1096
No	2493	2499	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	80	79	159
Baseline	2964	2965	5929

End points

End points 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	

Primary: Disease free survival

End point title	Disease free survival
End point description:	
End point type	Primary
End point timeframe: 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: 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 ^[1]
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 ^[2]
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
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Dictionary used

Dictionary name	NCI CTC AE
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Dictionary version	3
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Reporting groups

Reporting group title	Patients with CTC AE assessment on 3 month arm
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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
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Reporting group description:

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

Serious adverse events	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 %

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

subjects affected / exposed	71 / 434 (16.36%)	100 / 434 (23.04%)	
occurrences (all)	118	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 go 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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported