Clinical trial results:
A GCIG Intergroup multicentre trial of open label carboplatin & paclitaxel +/- bevacizumab compared with oxaliplatin & capecitabine +/- bevacizumab as first line chemotherapy in patients with mucinous Epithelial Ovarian cancer (mEOC)

Summary

EudraCT number	2008-000837-23
Trial protocol	GB FI IT DK
Global end of trial date	31 July 2015

Results information

Result version number	v1 (current)
This version publication date	10 July 2019
First version publication date	10 July 2019
Summary attachment (see zip file)	Gynae Oncol 2019 (mEOC Gynae Onc 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	UCL/07/095

Additional study identifiers

ISRCTN number	ISRCTN83438782
ClinicalTrials.gov id (NCT number)	NCT01081262
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Gower Street, London, United Kingdom, WC1E 6BT
Public contact	Trial Co-ordinator, CR UK and UCL Cancer Trials Centre, University College London , ctc.meoc@ucl.ac.uk
Scientific contact	Trial Co-ordinator, CR UK and UCL Cancer Trials Centre, University College London , ctc.meoc@ucl.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	15 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The trial will have two main objectives:
1) To determine whether chemotherapy with oxaliplatin and capecitabine improves the survival of patients with mucinous ovarian cancer.
2) To determine whether bevacizumab improves the overall survival of patients with mucinous cancer.

Protection of trial subjects:

Patient safety was monitored through strict eligibility criteria, regular patient assessments during treatment and follow-up, dose modifications for treatment related toxicity, regular review of safety data by the Independent Data Monitoring Committee (IDMC) and Trial Management Group (TMG) and general trial oversight by the Trial Steering Committee (TSC). Patient data is stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 and the Data Protection Officer at UCL.

Background therapy:

mEOC is a randomised multicentre phase III factorial trial in chemotherapy naïve patients with mucinous ovarian carcinoma. Randomisation will be 1:1:1:1

1) Carboplatin + Paclitaxel: Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, day 1; Paclitaxel 175mg/m2 IV, day 1
Patients will be treated every 3 weeks (1 cycle) for 6 cycles unless there is disease progression, intolerable toxicity or patients' refusal for further treatment.

2) Oxaliplatin + Capecitabine: Oxaliplatin 130mg/m2 IV, day 1; Capecitabine 850mg/m2 bd po, day 1-14
Patients will be treated every 3 weeks (1 cycle) for 6 cycles unless there is disease progression, intolerable toxicity or patients' refusal for further treatment.

3) Carboplatin + Paclitaxel with Bevacizumab: 6 cycles of chemotherapy plus bevacizumab (15mg/kg) given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

4) Oxaliplatin + Capecitabine with Bevacizumab: 6 cycles of chemotherapy plus bevacizumab given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

Evidence for comparator:

The combination of carboplatin plus paclitaxel preceded by tumour debulking surgery is currently the standard treatment for patients with advanced ovarian or primary peritoneal carcinoma.

The hypothesis of the study is that modifying treatment by using combinations that are useful in other mucinous tumours might improve outcomes for patients with mEOC. Mucinous carcinomas of the large bowel are commonly treated with a combination of oxaliplatin and fluoropyrimidine. Response rates of approximately 50% are consistently observed with oxaliplatin and infused 5-flurouracil or capecitabine, with a median survival of 16-20 months. In addition, the platinum analogue oxaliplatin is active in ovarian cancer and when combined with cyclophosphamide in first line treatment has similar activity to cisplatin plus cyclophosphamide. Recently, Pectasides and colleagues have used a combination of oxaliplatin plus fluorouracil (FOLFOX 4) in platinum-resistant, taxane-pretreated ovarian cancer and reported a 29% response rate. There is therefore, a sound rationale for conducting a randomised trial to evaluate the activity of oxaliplatin and capecitabine in mEOC and to use carboplatin-paclitaxel as the

control arm as this is currently the standard of care for histological subtypes of EOC.

A trial evaluating bevacizumab in ovarian cancer (ICON-7 & GOG 218) has shown positive results, so it is appropriate to examine this therapy specifically in patients with mucinous tumours. It is reasonable to incorporate anti-VEGF therapy in the mEOC study. The results of chemotherapy and bevacizumab have been positive in (mucinous) large bowel tumours, and the design of mEOC is based on the hypothesis that the treatment of mucinous tumours of the ovary is similar. Having a factorial trial is a highly efficient way of examining the two interventions (oxaliplatin + capecitabine, with bevacizumab) particularly because this is an uncommon tumour.

Actual start date of recruitment	04 March 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 34
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	50
EEA total number of subjects	34

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)	44
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were randomised into the trial between 04/03/2010-19/08/2013. Study closed to recruitment early due to poor recruitment, with 34 patients recruited in the UK and 16 patients in the USA giving a total of 50 out of the target 332 patients.

Pre-assignment

Screening details:

- CT or MRI scan
- Collection of histopathology slide
- Completion of histopathology report & patient diagnosed with mEOC
- Pre-treatment assessments
- Quality of Life questionnaires
- Urine dipstick for proteinuria
- Blood pressure
- Blood tests

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Carboplatin + Paclitaxel (Control)

Arm description:

Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, day 1
Paclitaxel 175mg/m2 IV, day 1

Arm type	Active comparator
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, in 250ml or 500ml of 5% dextrose according to local practice. Carboplatin will be given as an IV infusion over 30 minutes to 1 hour, or as per local practice. This will be administered on day 1.

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

Dosage and administration details:

Paclitaxel 175mg/m2 should be diluted in 500ml of 5% dextrose, or in 0.9% sodium chloride, according to the standard practice of the institution. The maximum Body Surface Area (BSA) for dose calculations will be 2.0m2. The paclitaxel should be administered via a non-PVC giving set and connectors incorporating a filter 0.22m. Paclitaxel should be given as an IV infusion over 3 hours. This will be administered on day 1.

Arm title	Oxaliplatin + Capecitabine

Arm description:

Oxaliplatin 130mg/m2 IV, day 1
Capecitabine 850mg/m2 bd po, day 1-14

Patients will be treated every 3 weeks (1 cycle) for 6 cycles unless there is disease progression, intolerable toxicity or patients' refusal for further treatment.

Arm type	Experimental
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:

The maximum BSA for dose calculations for oxaliplatin will be 2.0m2.
Prior to oxaliplatin administration, line must be flushed with 5% dextrose.
Oxaliplatin 130mg/m2 diluted in 250ml to 500ml of 5% dextrose will be given as an IV infusion over 2 to 6 hours. On completion of oxaliplatin the line should be flushed with 5% dextrose. A longer infusion time is recommended if patients experience minor hypersensitivities and vein pain. In addition use of an electric heat pad over the vein throughout the infusion may help to ease vein pain.

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

Dosage and administration details:

Capecitabine comes in tablets of 150mg and 500mg. The capecitabine dose is rounded to the nearest achievable dose using a capecitabine dose-banding table. The tablets are to be swallowed with water and taken within 30 minutes of a meal, approximately every 12 hours. If a patient has any difficulty swallowing, the tablets may be crushed and dissolved in water.

Arm title	Carboplatin + Paclitaxel + Bevacizumab

Arm description:

6 cycles of chemotherapy plus bevacizumab (15mg/kg) given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

Arm type	Experimental
Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, in 250ml or 500ml of 5% dextrose according to local practice. Carboplatin will be given as an IV infusion over 30 minutes to 1 hour, or as per local practice. This will be administered on day 1.

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

Dosage and administration details:

Paclitaxel 175mg/m2 should be diluted in 500ml of 5% dextrose, or in 0.9% sodium chloride, according to the standard practice of the institution. The maximum Body Surface Area (BSA) for dose calculations will be 2.0m2. The paclitaxel should be administered via a non-PVC giving set and connectors incorporating a filter 0.22m. Paclitaxel should be given as an IV infusion over 3 hours. This will be administered on day 1.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

When given with chemotherapy; Bevacizumab 15mg/kg IV:
- First cycle infused over 90 minutes
- If no problems then second cycle infused over 60 minutes
- If no problems then third and subsequent cycles infused over 30 minutes

When given alone:
- Bevacizumab 15mg/kg IV over 30 minutes (or fastest rate given previously).

Arm title	Oxaliplatin + Capecitabine + Bevacizumab

Arm description:

6 cycles of chemotherapy plus bevacizumab given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

Arm type	Experimental
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:

The maximum BSA for dose calculations for oxaliplatin will be 2.0m2.
Prior to oxaliplatin administration, line must be flushed with 5% dextrose.
Oxaliplatin 130mg/m2 diluted in 250ml to 500ml of 5% dextrose will be given as an IV infusion over 2 to 6 hours. On completion of oxaliplatin the line should be flushed with 5% dextrose. A longer infusion time is recommended if patients experience minor hypersensitivities and vein pain. In addition use of an electric heat pad over the vein throughout the infusion may help to ease vein pain.

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

Dosage and administration details:

Capecitabine comes in tablets of 150mg and 500mg. The capecitabine dose is rounded to the nearest achievable dose using a capecitabine dose-banding table. The tablets are to be swallowed with water and taken within 30 minutes of a meal, approximately every 12 hours. If a patient has any difficulty swallowing, the tablets may be crushed and dissolved in water.

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

Dosage and administration details:

When given with chemotherapy; Bevacizumab 15mg/kg IV:
- First cycle infused over 90 minutes
- If no problems then second cycle infused over 60 minutes
- If no problems then third and subsequent cycles infused over 30 minutes

When given alone:
- Bevacizumab 15mg/kg IV over 30 minutes (or fastest rate given previously).

Number of subjects in period 1	Carboplatin + Paclitaxel (Control)	Oxaliplatin + Capecitabine	Carboplatin + Paclitaxel + Bevacizumab
Started	13	13	11
Completed	13	13	11

Number of subjects in period 1	Oxaliplatin + Capecitabine + Bevacizumab
Started	13
Completed	13

Baseline characteristics

Reporting groups	
Reporting group title	Carboplatin + Paclitaxel (Control)
Reporting group description:	
Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, day 1 Paclitaxel 175mg/m2 IV, day 1	

Reporting group title	Oxaliplatin + Capecitabine
Reporting group description:	
Oxaliplatin 130mg/m2 IV, day 1 Capecitabine 850mg/m2 bd po, day 1-14 Patients will be treated every 3 weeks (1 cycle) for 6 cycles unless there is disease progression, intolerable toxicity or patients' refusal for further treatment.	

Reporting group title	Carboplatin + Paclitaxel + Bevacizumab
Reporting group description:	
6 cycles of chemotherapy plus bevacizumab (15mg/kg) given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.	
Reporting group title	Oxaliplatin + Capecitabine + Bevacizumab
Reporting group description:	
6 cycles of chemotherapy plus bevacizumab given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.	

Reporting group values	Carboplatin + Paclitaxel (Control)	Oxaliplatin + Capecitabine	Carboplatin + Paclitaxel + Bevacizumab
Number of subjects	13	13	11
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	12	13	10
From 65-84 years	1	0	1
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	13	13	11
Male	0	0	0

Reporting group values	Oxaliplatin + Capecitabine + Bevacizumab	Total	
Number of subjects	13	50	
Age categorical Units: Subjects			
In utero	0	0	

Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	9	44	
From 65-84 years	4	6	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	13	50	
Male	0	0	

Subject analysis sets

Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

These are the 50 patients who started the study drug.

Reporting group values	Safety analysis		
Number of subjects	50		
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)	44		
From 65-84 years	6		
85 years and over	0		
Gender categorical Units: Subjects			
Female	50		
Male	0		

End points

End points reporting groups

Reporting group title	Carboplatin + Paclitaxel (Control)

Reporting group description:

Carboplatin AUC 5 or AUC 6 (depending on whether GFR is measured or calculated) IV, day 1
Paclitaxel 175mg/m2 IV, day 1

Reporting group title	Oxaliplatin + Capecitabine

Reporting group description:

Oxaliplatin 130mg/m2 IV, day 1
Capecitabine 850mg/m2 bd po, day 1-14

Patients will be treated every 3 weeks (1 cycle) for 6 cycles unless there is disease progression, intolerable toxicity or patients' refusal for further treatment.

Reporting group title	Carboplatin + Paclitaxel + Bevacizumab

Reporting group description:

6 cycles of chemotherapy plus bevacizumab (15mg/kg) given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

Reporting group title	Oxaliplatin + Capecitabine + Bevacizumab

Reporting group description:

6 cycles of chemotherapy plus bevacizumab given on day 1 every three weeks, followed by 12 cycles of bevacizumab alone given on day 1 every three weeks.

Subject analysis set title	Safety analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

These are the 50 patients who started the study drug.

Primary: Progression free survival

End point title	Progression free survival[1]

End point description:

End point type	Primary

End point timeframe:

Progression free survival at 36 months:
Paclitaxel + carboplatin: 54%
Oxaliplatin + capecitabine: 31%
Paclitaxel + carboplatin + bevacizumab: 36%
Oxaliplatin + capecitabine+ bevacizumab: 46%

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The trial was stopped early due to poor recruitment, and only recruited 50 out of a total of 332 patients, no firm conclusions about best treatment options can be made.

End point values	Carboplatin + Paclitaxel (Control)	Oxaliplatin + Capecitabine	Carboplatin + Paclitaxel + Bevacizumab	Oxaliplatin + Capecitabine + Bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	11	13
Units: Percentage				
median (full range (min-max))	54 (27 to 81)	31 (6 to 56)	36 (8 to 64)	46 (19 to 73)

Statistical analyses

No statistical analyses for this end point

Primary: Overall survival

End point title	Overall survival[2]

End point description:

End point type	Primary

End point timeframe:

Overall survival at 36 months:
Paclitaxel + Carboplatin: 54%
Oxaliplatin + Capecitabine: 46%
Paclitaxel + Carboplatin + bevacizumab: 33%
Oxaliplatin + Capecitabine + bevacizumab: 54%

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The trial was stopped early due to poor recruitment, and only recruited 50 out of a total of 332 patients, no firm conclusions about best treatment options can be made.

End point values	Carboplatin + Paclitaxel (Control)	Oxaliplatin + Capecitabine	Carboplatin + Paclitaxel + Bevacizumab	Oxaliplatin + Capecitabine + Bevacizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	13	13	11	13
Units: Percentage				
median (full range (min-max))	54 (27 to 81)	46 (19 to 73)	33 (4 to 62)	54 (27 to 81)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: From informed consent to 30 days post last trial treatment administrtion.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The trial was stopped early due to poor recruitment, and only recruited 50 out of a total of 332 patients. reporting of available adverse events is in the scientific publication attached.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 January 2009	- Change of PI at existing site: Derbyshire Royal Infirmary - Protocol v2.0, PIS v2.0, Consent Form v2.0, GP letter v2.0, Patient card v2.0, FACT-O TOI Questionnaire, FACT/GOG-NTX Subscale Questionnaire, EQ-5D Questionnaire - Inclusion of bevacizumab to the trial: updates to title, introduction, inclusion/exclusion criteria, treatment schedules, follow up schedules, safety reporting, and statistical considerations in the protocol. - The FACT-O quality of life (QoL) questionnaire is no longer being used to assess quality of life. The FACT-O-TOI and FACT/GOG-NTX Subscale Questionnaire will now be used. - Changes have been made to the pathology section of the protocol; further detail has been provided regarding the central pathology review process, and the process for requesting and obtaining tumour samples for future biological research has been explained. - Appendices relating to expected adverse events associated with oxaliplatin and capecitabine have been re-ordered, so that the expected adverse events of oxaliplatin are now given before the expected adverse events of capecitabine. This is to ensure consistency throughout the protocol in terms of ordering of information.
26 May 2009	- Protocol v3.0, dated 18/05/2009, PIS v3.0, dated 18/05/2009, Consent Form v3.0 dated 18/05/2009, GP letter v3.0 dated 18/05/2009 - The dose of bevacizumab has been increased from 7.5mg/kg to 15mg/kg. This decision was taken following extensive discussion with International and UK collaborators. - Inclusion criteria; regarding creatinine clearance has changed. The creatinine clearance must now be ≥50ml/min for both calculations and measurements of GFR. - Changes have been made to the CT/MRI scanning schedule. CT scans will now be carried out every 3 months during year 1. - Quality of life assessments will now be carried out at: baseline, post cycle 3 of chemotherapy, one-month post cycle 6 of chemotherapy, 6 months post chemotherapy, at week 58 safety follow up visit, 6 months post week 58, and then annually thereafter. - Patients who are not receiving bevacizumab will now be telephoned midway between each 6-weekly visit during weeks 18-54. - Guidelines have been changed to allow patients who come off trial treatment as a result of unacceptable toxicity, or disease progression, to be treated according to local practice.
26 October 2009	- Additional sites & clinicians - Change of site information - PI changes
22 January 2010	- Protocol v4, PIS v4, Consent Form v4 – updated with new CTCAE v4 and RECIST 1.1 information - Change of site information, PI changes - Study documentation has been revised to include the new CTCAE v4 and RECIST 1.1 information, replacing CTCAE v3 and RECIST 1.0. - One exclusion criteria has been added to the protocol "Fertile women of childbearing potential not willing to use adequate contraception for the duration of trial treatment and at least 6 months after" - Updates to information related to patient identifiers, data protection, the collection of informed consent forms and a defined end of trial date.
22 March 2010	- Additional sites & clinicians - PI change

07 December 2010	- New Protocol v5, PIS v5, Consent Form v5 - Urgent Safety measure: Roche Products Ltd and MHRA have issued a safety warning regarding Bisphosphonates and Bevacizumab (Avastin) on 30/11/2010. - Patients are excluded from the trial if they have taken bisphosphonates - Precautions for use of Bevacizumab. Bisphosphonates must not be administered during treatment with bevacizumab or sequentially after treatment. There is a risk of Osteonecrosis of the jaw linked with bisphosphonate use and bevacizumab, although this is very rare (less than 1 in 10,000 patients). - Safety Update added as reference - Osteonecrosis of the jaw added as a very rare expected event - Addition of information on Bisphosphonates (based on Roche Safety Update, 30.11.2010) "Bevacizumab could interact with bisphosphonates which are used to control bone thinning, causing necrosis of the jaw. Bisphosphonates will not be used for patients on this trial."
12 January 2011	- New Protocol v6, PIS v6, Consent Form v6 - New sites, PI change - new exclusion criteria, any patients taking warfarin will be excluded from the trial. - Roche confirmed that the Bevacizumab can be given before or after chemotherapy for both the first dose and for all subsequent doses. The wording for the order of treatment was amended to make this a recommendation rather than a stipulation. - Roche requested to shorten the length of time from dispensing Bevacizumab to patient treatment. The protocol now states that Bevacizumab should be given within an 8 hour period. This can be extended to 24 hours if prepared in validated and aseptic conditions. - clinicians may recommend that the patient skip the first cycle of Bevacizumab if they feel that the patient's wound is not completely healed. - addition of possible side-effects that may occur after a Bevacizumab infusion. This has been incorporated into the Protocol as a response to the Roche Products Limited Safety Update released 29/04/2010. - dose modification changes for carboplatin and paclitaxel arm and oxaliplatin and capecitabine arm.
30 January 2012	- New Protocol v7, New Pregnancy Monitoring PIS v1, Consent Form v1, Bevacizumab Investigators Brochure 19th Version - revised the following exclusion criteria: c) Patients with synchronous primary endometrial carcinoma, or a past history of primary endometrial carcinoma are excluded unless the endometrial carcinoma is Grade 1 or 2, stage 1A (FIGO 2009). d) Malignancies other than ovarian cancer within 5 years prior to randomisation, except for adequately treated carcinoma in situ of the cervix and/or basal cell skin cancer and/or early endometrial carcinoma as specified above. Patients may have received previous adjuvant chemotherapy for other malignancies e.g. breast or colorectal carcinoma if diagnosed over 5 years ago with no evidence of subsequent recurrence. Mucinous colorectal cancer can be included but the pathologist must be certain that the ovarian cancer is a new primary tumour. - Additional dose modification guidelines for febrile neutropaenia and haematological toxicities - Specific adverse events of special interest to be reported to Roche - Patients who experience Grade 4 fistula or patients with tracheoesophageal (TE) fistula or intracranial bleeding should not receive further bevacizumab treatment.
23 October 2012	- Protocol v8: administrative changes relating to dose banding variance, capecitabine dose banding and UCL CTC email addresses - Update indemnity section in protocol/PIS - Extend time from surgery to randomisation - Change eligibility criteria FIGO Stage II-IV to new or relapsed. - Allow patients who have had previous chemotherapy for rectal cancer (if diagnosed over 5 years ago with no evidence of subsequent recurrence). Exclude patients who have had previous chemotherapy for ovarian cancer.

06 June 2013	Temporary Halt to recruitment
14 June 2013	Request to restart Trial after a temporary halt.
23 July 2013	Update to patient information sheet (v8) and consent form (v8)
14 February 2014	Protocol v9 amendment and annual update to IB - Revised IB submitted - Protocol updated in line with revised IB (v21). Further minor administrative changes and clarifications added (i.e. RECIST table amended to v1.1, as well as updates in line with the CTC protocol template). - updated to include new information that rarely, bevacizumab may increase risk of necrotising fasciitis, including fatal cases, and that bevacizumab is associated with an increased risk of arterial thromboembolism in patients with medical history of diabetes mellitus. - Necrotising fasciitis added to list of adverse events. - caution when treating patients with a medical history of diabetes - Annex 1 form updated with new trial contact person details for importing in to EudraCT (submitted to the MHRA only)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported