Clinical trial results:
Bevacizumab And Combination Chemotherapy in rectal cancer Until Surgery: A Phase II, Multicentre, Open-label, Randomised Study of Neoadjuvant Chemotherapy and Bevacizumab in Patients with MRI defined High-Risk Cancer of the Rectum

Summary

EudraCT number	2010-022754-17
Trial protocol	GB
Global end of trial date	14 February 2019
Results information	
Result version number	v1 (current)
This version publication date	22 December 2019
First version publication date	22 December 2019
Summary attachment (see zip file)	BACCHUS (BACCHUS_Heliyon_20180922.pdf)

Trial information

Trial identification	
Sponsor protocol code	UCL/09/0176
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01650428
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	University College London
Sponsor organisation address	90 Tottenham Court Road, London, United Kingdom,
Public contact	Sarah Pearce, University College London, 0207 6799392, ctc.bacchus@ucl.ac.uk
Scientific contact	Sarah Pearce, University College London, 0207 6799392, ctc.bacchus@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	10 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 February 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principal research question is to see how effective the two different treatment arms are. Efficacy will be measured by examining tissue removed at surgery to see how many patients have a pathological complete response; that is - how many patients do not have any visible tumour left, even when looking through a microscope.

Protection of trial subjects:

The risks for patients in this trial were similar to those for any patient undergoing chemotherapy treatment.
The chemotherapy regimens used were new and intense but consideration was given to this when writing the protocol. The eligibility criteria were stringent to ensure patients were fit enough to receive treatment, assessments during and after trial treatment were comprehensive and detailed guidance was given in the protocol for dose modifications if/when toxicity from the chemotherapy occurred.
Adverse events pertaining to the administration of these drugs were closely monitored throughout the trial. Each patient's GP was informed of their participation and asked to report all serious side effects immediately to the research team at site. Patient cards were also issued to the patients in case of emergencies, which contained information about the study.
A risk assessment was performed for this trial and an appropriate level of monitoring was carried out including the monitoring of patient safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2012
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: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	16
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment start date: 29/05/2013
Recruitment end date: 08/09/2015
Total Number of sites: 15

Pre-assignment

Screening details:

522 patients screened.
Patients were excluded for 1 of the following reasons: not 18-70 years of age, not 18-75 years of age (20/08/2014,age range extended) Pelvic MRI disease not meet eligibility criteria. Metastatic disease. Tumour not 4-12cm from anal verge. Previous radiotherapy. Recent surgery. WHO PS >1, Patient refusal. Clinical decision.

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	Arm A

Arm description:

FOLFOX + bevacizumab:
- Bevacizumab 5 mg/kg IV over 30 – 90 minutes (cycles 1 – 5)
- Oxaliplatin 85 mg/m2 IV over 2 hours
- Folinic acid 350 mg IV over 2 hours
- 5FU 3200 mg/m2 IV continuous infusion over 48 hours

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg on day 1 of each cycle, 25 mg/kg in total over 5 cycles

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:

85 mg/m2 on day 1 of each cycle, 510 mg/m2 in total over 6 cycles

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

Dosage and administration details:

3200 mg/m2 as continuous infusion over 48 hours starting on day 1 of each cycle, 19200 mg/m2 in total over 6 cycles

Arm title	Arm B

Arm description:

FOLFOXIRI + Bevacizumab. Given every 2 weeks for 12 weeks (6 cycles)
- Bevacizumab 5 mg/kg IV over 30 – 90* minutes (cycles 1 – 5 only)
- Irinotecan 165 mg/m2 IV over 1 hour
- Oxaliplatin 85 mg/m2 IV over 2 hours
- 5FU 3200 mg/m2 IV continuous infusion over 48 hours

Arm type	Active comparator
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

5 mg/kg on day 1 of each cycle, 25 mg/kg in total over 5 cycles

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:

85 mg/m2 on day 1 of each cycle, 510 mg/m2 in total over 6 cycles

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

Dosage and administration details:

3200 mg/m2 as continuous infusion over 48 hours starting on day 1 of each cycle, 19200 mg/m2 in total over 6 cycles

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

Dosage and administration details:

165 mg/m2 on day 1 of each cycle, 990 mg/m2 in total over 6 cycles

Number of subjects in period 1	Arm A	Arm B
Started	10	10
Completed	10	10

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	20	20	
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)	16	16	
From 65-84 years	4	4	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	8	8	
Male	12	12	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

FOLFOX + bevacizumab:
- Bevacizumab 5 mg/kg IV over 30 – 90 minutes (cycles 1 – 5)
- Oxaliplatin 85 mg/m2 IV over 2 hours
- Folinic acid 350 mg IV over 2 hours
- 5FU 3200 mg/m2 IV continuous infusion over 48 hours

Reporting group title	Arm B

Reporting group description:

FOLFOXIRI + Bevacizumab. Given every 2 weeks for 12 weeks (6 cycles)
- Bevacizumab 5 mg/kg IV over 30 – 90* minutes (cycles 1 – 5 only)
- Irinotecan 165 mg/m2 IV over 1 hour
- Oxaliplatin 85 mg/m2 IV over 2 hours
- 5FU 3200 mg/m2 IV continuous infusion over 48 hours

Primary: Pathological complete response (pCR) in the histological specimen

End point title	Pathological complete response (pCR) in the histological specimen

End point description:

The primary endpoint for this trial is the pathological complete response rate (pCR). The proportion of patients in each arm who achieve a pCR will be presented, along with a 95% confidence interval (CI). pCR will be assessed after surgery. Within each group the achieved pCR rate will be compared to the rate achieved by radiotherapy alone (5%).
The study is powered on the assumption that a substantial proportion of patients will have a pCR. It is well recognised that patients who have a complete clinical response both on imaging and clinical examination will from time to time refuse surgery. For the purpose of this study, patients who have a sustained clinical complete response at 12 months will be considered the same as a patient with a complete pathological response. In contrast, patients with a transient clinical response where local endoluminal or pelvic relapse is observed within this 12 month timeframe will not.

End point type	Primary

End point timeframe:

pCR will be assessed after surgery.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage				
pCR	0	2		
Non-pCR	10	8		

Statistical analyses

Statistical analysis title	Pathological Complete response rate

Statistical analysis description:

The primary endpoint for this trial is the pathological complete response rate (pCR). The proportion of patients in each arm who achieve a pCR will be presented, along with a 95% confidence interval (CI). pCR will be assessed after surgery. The analysis was not powered for a direct comparison between treatment groups. The analysis was powered to compare the pCR rates in each group with historical controls data (pCR rate in radiotherapy alone in historical controls is 5%).

Comparison groups	Arm A v Arm B
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[1]
Method	single proportion in each treatment
Parameter estimate	single proportion in FOLFOXIRI arm
Point estimate	0.22
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.04
upper limit	0.55

Notes:

[1] - A'Hern single stage design, ie, single proportion test

Secondary: RECIST response rate

End point title	RECIST response rate

End point description:

RECIST response rate will be presented as percentages with corresponding 95% CIs. Time to event outcomes will be estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

This will be assessed after chemotherapy has ended. Complete response and Partial response will be considered as responses. The best response during chemotherapy will be given for each patient.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[2]	10[3]		
Units: Percentage				
Complete Response	11	30		
Partial Response	88	40		
Stable Disease	0	30		

Notes:

[2] - Measured in Percentage

[3] - Measured in Percentage

Statistical analyses

No statistical analyses for this end point

Secondary: CRM negative resection rate

End point title	CRM negative resection rate

End point description:

CRM negative resection rate: those with a resection distance >1mm amongst those having surgery.

End point type	Secondary

End point timeframe:

Post surgery. Those with a resection distance >1mm amongst those having surgery.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage				
RO - Resection	70	100		
R2 Resection	10	0		
Not available	20	0		

Statistical analyses

No statistical analyses for this end point

Secondary: T and N stage downstaging

End point title	T and N stage downstaging

End point description:

This will examine T and N stage to assess whether stage has worsened from baseline to post-treatment. A patient will be considered to have downstaged if i) both T and N stage decrease; or ii) either T or N stage decreases and the other remains stable.

End point type	Secondary

End point timeframe:

From baseline to post-treatment.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage				
Downstaged	60	70		
Maintained T and N Stage	10	10		
Not evaluable	30	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Defined as time from randomisation to disease progression or death, whichever occurs first. Disease progression will be assessed by the RECIST criteria at pre-cycle 4 and post-treatment.

End point type	Secondary

End point timeframe:

Disease progression will be assessed at pre-cycle 4 and post-treatment.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[4]	10[5]		
Units: months				
number (not applicable)				
2 year Progresssion Free Survial	80	100		
Deaths	20	0		

Notes:

[4] - percentage

[5] - percentage

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival

End point title	Disease free survival

End point description:

Defined as the time from surgery with complete resections (R0) to the occurrence of relapse, second colorectal primary or death from any cause, whichever occurs first. Only subjects who have a complete resection (R0) will be included in this analysis. Patients who are alive, without recurrence and with no secondary colorectal cancer at the time of cut-off will be right-censored at the most recent date of assessment.

End point type	Secondary

End point timeframe:

From surgery to the occurrence of relapse, second colorectal primary or death from any cause, whichever occurs first.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[6]	10[7]		
Units: months				
number (not applicable)				
Disease Free Survival	71	100		

Notes:

[6] - measured as percentage

[7] - measured as percentage

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Defined as the time from study entry until death. The OS of all subjects and of the subgroup who had complete resection (R0) will be calculated.

End point type	Secondary

End point timeframe:

Randomisation to death.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Months				
number (not applicable)				
Deaths	20	0		
Alive	80	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Local control

End point title	Local control

End point description:

This will be assessed just for those patients who attain a CRM negative resection. This will be measured from date of surgery until local failure.

End point type	Secondary

End point timeframe:

This will be measured from date of surgery until local failure.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7[8]	10[9]		
Units: percentage				
Progressed	28	0		
Not Progressed	71	100		

Notes:

[8] - measured as percentage

[9] - measured as percentage

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year colostomy rate

End point title	1-year colostomy rate

End point description:

This will be assessed post-surgery. The proportion of patients with an unreversed stoma one-year after surgery will be considered to have a colostomy at 1-year.

End point type	Secondary

End point timeframe:

Up to one year post surgery.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[10]	4[11]		
Units: percentage				
Stoma	0	50		
No Stoma	100	50		

Notes:

[10] - measured as percentage

[11] - measured as percentage

Statistical analyses

No statistical analyses for this end point

Secondary: Chemotherapy compliance

End point title	Chemotherapy compliance

End point description:

Dose reductions and dose delays to all chemotherapy agents will be recorded.

End point type	Secondary

End point timeframe:

Start to end of treatment

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage				
Dose Reduction (any reason)	40	60		
Dose Omission (any reason)	10	10		
Without Dose Omission	90	90		
Without Dose Reduction	60	40		

Statistical analyses

No statistical analyses for this end point

Secondary: Tumour Regression Grade

End point title	Tumour Regression Grade

End point description:

End point type	Secondary

End point timeframe:

Results from the post-resection tumour sample

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: percentage				
Total Response	0	10		
Good Regression	20	20		
Moderate Regression	20	40		
Minimal Regression	30	10		
No Regression	10	10		
Not Reported	20	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events that occurred between informed consent and 3 months after surgery to remove the rectal tumour were recorded.

Adverse event reporting additional description:

Adverse events pertaining to the study drugs were closely monitored throughout the trial. Patient's GP were informed of their participation and asked to report all serious side effects immediately to sites. Patient cards and diaries were also issued to patients and reviewed before each treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Arm A

Reporting group description: -

Reporting group title	Arm B

Reporting group description: -

Serious adverse events	Arm A	Arm B	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Depression			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Arm A	Arm B	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)	10 / 10 (100.00%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	4 / 10 (40.00%)	5 / 10 (50.00%)	
occurrences (all)	2	6	

Hypotension			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Constipation			
subjects affected / exposed	4 / 10 (40.00%)	8 / 10 (80.00%)	
occurrences (all)	3	8	
Fatigue			
subjects affected / exposed	8 / 10 (80.00%)	10 / 10 (100.00%)	
occurrences (all)	8	10	
Fever			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Reproductive system and breast disorders			
Ejaculation disorder			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pelvic pain			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Epistaxis			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Laryngospasm			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pharyngeal mucositis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
sore thoat			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	2	3	
Alanine aminotransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	3 / 10 (30.00%)	
occurrences (all)	4	4	
Alkaline phosphatase increased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	
occurrences (all)	1	3	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	
occurrences (all)	3	3	
Blood bilirubin increased			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Creatinine urine increased			

subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	2	5	
Lymphocyte count decreased			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	
occurrences (all)	1	3	
Lymphocyte count increased			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	5 / 10 (50.00%)	8 / 10 (80.00%)	
occurrences (all)	5	8	
Platelet count decreased			
subjects affected / exposed	3 / 10 (30.00%)	4 / 10 (40.00%)	
occurrences (all)	3	4	
Weight loss			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
White blood cell count decreased			
subjects affected / exposed	3 / 10 (30.00%)	5 / 10 (50.00%)	
occurrences (all)	3	5	
Injury, poisoning and procedural complications			
Wound complication			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	2	2	
Wound dehiscence			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Atrial fibrillation			

subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	2 / 10 (20.00%)	4 / 10 (40.00%)	
occurrences (all)	2	4	
Headache			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Paresthesia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 10 (40.00%)	4 / 10 (40.00%)	
occurrences (all)	6	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 10 (20.00%)	2 / 10 (20.00%)	
occurrences (all)	5	10	
Bone Marrow Hypocellular			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	1 / 10 (10.00%)	2 / 10 (20.00%)	
occurrences (all)	1	2	
Leukocytosis			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Eye disorders			
Blurred Vision			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Abdominal Pain			

subjects affected / exposed	5 / 10 (50.00%)	9 / 10 (90.00%)	
occurrences (all)	6	10	
Anal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Colonic obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	7 / 10 (70.00%)	8 / 10 (80.00%)	
occurrences (all)	7	8	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
mucositis oral			
subjects affected / exposed	3 / 10 (30.00%)	3 / 10 (30.00%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed	5 / 10 (50.00%)	8 / 10 (80.00%)	
occurrences (all)	5	8	
Rectal haemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
rectal pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Small intestine obstruction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	6 / 10 (60.00%)	5 / 10 (50.00%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 10 (0.00%)	4 / 10 (40.00%)	
occurrences (all)	0	4	

Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Urinary retention			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Catheter infection			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Pelvic infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Sepsis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	3	

Wound infection			
subjects affected / exposed	0 / 10 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Metabolism and nutrition disorders			
Anorexia nervosa			
subjects affected / exposed	2 / 10 (20.00%)	4 / 10 (40.00%)	
occurrences (all)	2	5	
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)	3 / 10 (30.00%)	
occurrences (all)	1	3	
Hypokalaemia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 10 (10.00%)	
occurrences (all)	1	2	
Hyponatraemia			
subjects affected / exposed	2 / 10 (20.00%)	1 / 10 (10.00%)	
occurrences (all)	2	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2013	Minimum time from finishing bevacizumab treatment to having surgery changed from 6 wks to 8 wks. Volume of blood collected increased from 9mls to 24 mls at each time-point. Safety information for bevacizumab added for necrotising faciitis & thromboembolisms. PIS: Contraceptive advice clarified. Additional safety information added from updated SPCs. Information about MRI scans added ICF: Additional MRI scans are now optional for patients as sites with the facilities
11 July 2014	Inclusion criteria: Increased upper age limit of eligible patients from 70 to 75
17 November 2014	Inclusion criteria: To include T4b patients Exclusion Criteria: Bisphosphonates wording changed Bisphosphonates added to list of concomitant medications
05 March 2015	Inclusion criteria: T3 tumours extending (≥ 4 mm), beyond the muscularis propria N0–N2 Tumours (involving or threatening the peritoneal surface) OR presence of macroscopic extramural venous invasion (V2 disease) AND for tumours below the peritoneal reflection, the primary tumour or involved lymph node (on MRI) must be >1 mm from the mesorectal fascia Exclusion Criteria: Circumferential resection margins has been removed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30258994