

**Clinical trial results:**

A Phase III, randomised, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy for patients with locally advanced/metastatic biliary tract cancers previously treated with cisplatin / gemcitabine chemotherapy

Summary

EudraCT number	2013-001812-30
Trial protocol	GB
Global end of trial date	04 January 2019

Results information

Result version number	v1 (current)
This version publication date	19 May 2023
First version publication date	19 May 2023

Trial information**Trial identification**

Sponsor protocol code	CFTSp048
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01926236
WHO universal trial number (UTN)	-
Other trial identifiers	Funders reference number (CTAAC): A16281

Notes:

Sponsors

Sponsor organisation name	The Christie NHS Foundation Trust
Sponsor organisation address	550 Wilmslow Road, Manchester, United Kingdom, M20 4BX
Public contact	Tim Macdonald, Manchester Clinical Trials Unit, ABC06@manchester.ac.uk
Scientific contact	Prof J Valle, The Christie NHS Foundation Trust, the-christie.sponsoredresearch@nhs.net

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	04 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2019
Global end of trial reached?	Yes
Global end of trial date	04 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether fit patients (with performance score of 0-1) with advanced biliary tract cancer (ABC) benefit from chemotherapy in the second-line setting (after prior therapy with cisplatin and gemcitabine) in terms of their overall length of survival.

Protection of trial subjects:

Trial conducted to full Good Clinical Practice standard. All potential risks involved with study participation and trial treatment were communicated in the patient information sheets. Subjects were assigned a unique trial to ensure participant anonymisation. Patient personal data was regarded as highly confidential. Any identifiable information collected at a study centre was held in strictest confidence and not made available to the clinical trial unit collating the data, nor released to into the public domain.

Patients could be withdrawn from chemotherapy treatment prior to completion of all cycles due to: Intolerable toxicity/ adverse event/ intercurrent illness. All adverse events were treated with maximum supportive care (including withholding administration of the agent suspected of causing the adverse event where required).

On-site trial monitoring was permitted in order to verify that the rights and well-being of patients/participants were protected, and to evaluate whether the conduct of the trial within a given institution was compliant with the currently approved protocol, GCP and with the applicable regulatory requirements.

Background therapy:

Active symptom control: biliary drainage, antibiotics, analgesia, steroids, anti-emetics and any other palliative treatment for symptom control (example: palliative radiotherapy, blood transfusion etc). Patients may receive all concomitant therapy deemed to provide adequate supportive care at the investigator's discretion. However, the use of experimental drugs were not permitted until at least 28 days after the completion of chemotherapy.

Evidence for comparator:

Three groups of agents have broadly shown activity in biliary tract cancer in retrospective and prospective trials: gemcitabine, fluoropyrimidines and platinum agents. Moreover, the sensitivity to a platinum agent has been recently confirmed in the phase III ABC-02 trial, in which cisplatin and gemcitabine combination arm shown benefit in survival compared to gemcitabine alone. After progressing to a first line gemcitabine-based chemotherapy switching to a fluoropyrimidine-based schedule is considered appropriate.

A previous pooled analysis suggests that patients receiving doublet-chemotherapy have a greater benefit vs. monotherapy. Given the known platinum sensitivity (from ABC-02), it is anticipated that a 5-FU / platinum doublet is most likely to be effective. The third-generation platinum analogue oxaliplatin is known for its activity in several gastrointestinal tumours and a synergistic activity with a favourable toxicity profile seems to exist with its combination with 5FU.

In twenty-nine patients with locally advanced or metastatic BTC treated with single agent oxaliplatin an objective response rate of 20.6% was shown, thus oxaliplatin appears to be an active agent against BTC. Additional studies using Oxaliplatin/ 5FU based regimens for biliary tract tumours are available, with good results and acceptable toxicity. In 2008 a phase II trial in 28 patients (including pre-treated and chemotherapy-naïve) patients treated with FOLFOX achieved a response rate of 21.5% and median overall survival of 10 months. In another prospective analysis of sixteen patients diagnosed with ABC, FOLFOX achieved a disease control rate (PR + stable disease) of 56% and a median overall

survival of 9.5 months.

Actual start date of recruitment	01 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 162
Worldwide total number of subjects	162
EEA total number of subjects	162

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)	79
From 65 to 84 years	83
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment began in February 2014. 20 UK-only sites were involved in the study. The final participant was recruited in January 2018.

Pre-assignment

Screening details:

All pre-treatment evaluations were carried out before randomisation. All eligible patients were randomised, and all those allocated to Arm B started study treatment within 6 weeks of confirmed radiological progression.

Period 1

Period 1 title	Overall trial (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	ASC alone

Arm description:

Active Symptom Control alone

Arm type	Active Symptom Control
No investigational medicinal product assigned in this arm	

Arm title	ASC plus FOLFOX
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Arm description:

Active symptom control plus FOLFOX chemotherapy

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

Dosage and administration details:

Dose of 85mg/m². Patients allocated to receive chemotherapy will be seen for treatment every 2 weeks; chemotherapy will continue (in the absence of disease progression, intolerable toxicity or patient choice to withdraw) to a maximum of 12 cycles (6 months). Oxaliplatin administered in 250-500ml of glucose 5% over 2 hours, no other diluents must be used to prepare the oxaliplatin infusion for administration. Each chemotherapy treatment prepared and administered in a separate bag of diluent

Investigational medicinal product name	Fluorouracil
Investigational medicinal product code	
Other name	5FU, Adrucil
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous bolus use , Intravenous use, Solution for infusion , Solution for injection

Dosage and administration details:

400 mg/m² 5-10 minute bolus (day 1). 2400 mg/m² 46 hours continuous intravenous infusion (starting day 1, finishing day 2)

Investigational medicinal product name	L-folinic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use, Solution for infusion

Dosage and administration details:

175 mg (or folinic acid 350 mg). Two hours intravenous infusion (day1) concurrently with oxaliplatin infusion.

Number of subjects in period 1	ASC alone	ASC plus FOLFOX
Started	81	81
Completed	81	81

Baseline characteristics

Reporting groups

Reporting group title	ASC alone
Reporting group description: Active Symptom Control alone	
Reporting group title	ASC plus FOLFOX
Reporting group description: Active symptom control plus FOLFOX chemotherapy	

Reporting group values	ASC alone	ASC plus FOLFOX	Total
Number of subjects	81	81	162
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)	39	40	79
From 65-84 years	42	41	83
85 years and over	0	0	0
Age continuous			
Units: years			
median	65	65	
full range (min-max)	26 to 81	26 to 84	-
Gender categorical			
Units: Subjects			
Female	44	38	82
Male	37	43	80
Platinum sensitivity			
Units: Subjects			
Resistant or refractory	47	38	85
Sensitive	34	43	77
Albumin			
Units: Subjects			
<35 g/L	21	19	40
≥35 g/L	60	62	122
Disease stage			
Units: Subjects			
Locally advanced	15	14	29
Metastatic	66	67	133
Tumour site			
Units: Subjects			
Intrahepatic	38	34	72
Extrahepatic	19	26	45

Gallbladder	17	17	34
Ampulla	7	4	11
Histology			
Other included squamous, adenosquamous, and not specified.			
Units: Subjects			
Adenocarcinoma	74	73	147
Other	7	8	15
Grade of differentiation			
Units: Subjects			
Well	5	9	14
Moderately	41	37	78
Poorly	11	9	20
Not specified	23	26	49
Missing	1	0	1
ECOG performance status			
Units: Subjects			
00	28	25	53
01	52	55	107
Missing	1	1	2
Had previous surgery			
Units: Subjects			
Yes	38	34	72
No	43	47	90
Previous cisplatin and gemcitabine			
Units: Duration, months			
arithmetic mean	4.8	4.9	
full range (min-max)	2.9 to 5.3	2.8 to 5.5	-
Baseline CA19.9			
Baseline tumour marker data were available for 67 (ASC alone) and 68 (ASC plus FOLFOX) patients for CA19.9.			
Units: U/mL			
arithmetic mean	443	162	
full range (min-max)	46 to 5714	25 to 1903	-
Baseline carcinoembryonic antigen			
Baseline tumour marker data were available for 76 (ASC alone) and 76 (ASC plus FOLFOX) patients for carcinoembryonic antigen			
Units: U/mL			
arithmetic mean	6	6	
full range (min-max)	3 to 16	3 to 24	-
Baseline CA125			
Baseline tumour marker data were available for 71 (ASC alone) and 72 (ASC plus FOLFOX) patients for CA125.			
Units: U/mL			
arithmetic mean	42	52	
full range (min-max)	20 to 168	21 to 159	-

End points

End points reporting groups

Reporting group title	ASC alone
Reporting group description:	
Active Symptom Control alone	
Reporting group title	ASC plus FOLFOX
Reporting group description:	
Active symptom control plus FOLFOX chemotherapy	

Primary: Overall survival

End point title	Overall survival
End point description:	
End point type	Primary
End point timeframe:	from randomisation to death from any cause

End point values	ASC alone	ASC plus FOLFOX		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	81		
Units: months				
median (confidence interval 95%)	5.3 (4.1 to 5.8)	6.2 (5.4 to 7.6)		

Statistical analyses

Statistical analysis title	Overall Survival
Statistical analysis description:	
The study was powered to show a benefit in overall survival with the addition of FOLFOX to ASC in the intention-to-treat population. 148 death events were required for a hypothesised hazard ratio (HR) of 0.63 with 80% power and 5% two-sided α ; since minimal (<3%) loss to follow-up was envisaged, the required sample size was 162 patients.	
Comparison groups	ASC plus FOLFOX v ASC alone
Number of subjects included in analysis	162
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.97

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From informed consent and end of trial treatment. Since Active Symptom Control was provided until death/ end of trial, AEs were expected to be recorded up until patient death / end of trial.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	ASC plus FOLFOX
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Reporting group description: -

Reporting group title	ASC alone
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Reporting group description: -

Serious adverse events	ASC plus FOLFOX	ASC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	46 / 81 (56.79%)	39 / 81 (48.15%)	
number of deaths (all causes)	76	74	
number of deaths resulting from adverse events	7	4	
Vascular disorders			
Hypotension	Additional description: Hypotension		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thromboembolic event	Additional description: Thromboembolic event		
subjects affected / exposed	0 / 81 (0.00%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg oedema	Additional description: Leg oedema		

subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema	Additional description: Oedema		
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain	Additional description: Pain		
subjects affected / exposed	5 / 81 (6.17%)	6 / 81 (7.41%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Hallucinations	Additional description: Hallucinations		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture	Additional description: Hip fracture		

subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction	Additional description: Myocardial infarction		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular ischaemia	Additional description: Cerebrovascular ischaemia		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Febrile neutropenia		
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ascites	Additional description: Ascites		
subjects affected / exposed	2 / 81 (2.47%)	2 / 81 (2.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric outlet obstruction	Additional description: Gastric outlet obstruction		

subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleeding			
Additional description: Gastrointestinal bleeding			
subjects affected / exposed	0 / 81 (0.00%)	3 / 81 (3.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
Additional description: Diarrhoea			
subjects affected / exposed	3 / 81 (3.70%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	3 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
Additional description: Constipation			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
Additional description: Vomiting			
subjects affected / exposed	5 / 81 (6.17%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	3 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
Additional description: Nausea			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary event			
Additional description: Biliary event			
subjects affected / exposed	15 / 81 (18.52%)	16 / 81 (19.75%)	
occurrences causally related to treatment / all	2 / 15	0 / 17	
deaths causally related to treatment / all	0 / 1	0 / 2	
Liver failure			
Additional description: Liver failure			
subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Erythema subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Erythema		
	0 / 81 (0.00%)	1 / 81 (1.23%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Acute kidney injury		
	3 / 81 (3.70%)	0 / 81 (0.00%)	
	2 / 3	0 / 0	
	1 / 2	0 / 0	
Musculoskeletal and connective tissue disorders Rhabdomyolysis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Rhabdomyolysis		
	1 / 81 (1.23%)	0 / 81 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Infections and infestations Catheter-related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Catheter-related infection		
	2 / 81 (2.47%)	0 / 81 (0.00%)	
	0 / 2	0 / 0	
	0 / 0	0 / 0	
Infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Infection		
	13 / 81 (16.05%)	5 / 81 (6.17%)	
	8 / 13	0 / 5	
	1 / 1	0 / 2	
Metabolism and nutrition disorders Diabetic ketoacidosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Diabetic ketoacidosis		
	1 / 81 (1.23%)	0 / 81 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Dehydration		
	0 / 81 (0.00%)	1 / 81 (1.23%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Hyponatremia	Additional description: Hyponatremia		

subjects affected / exposed	0 / 81 (0.00%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphatamia			
Additional description: Hypophosphatamia			
subjects affected / exposed	1 / 81 (1.23%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcemia			
Additional description: Hypercalcemia			
subjects affected / exposed	2 / 81 (2.47%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	0 / 2	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	ASC plus FOLFOX	ASC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	80 / 81 (98.77%)	78 / 81 (96.30%)	
Vascular disorders			
Hypotension			
Additional description: Hypotension			
subjects affected / exposed	1 / 81 (1.23%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Hypertension			
Additional description: Hypertension			
subjects affected / exposed	14 / 81 (17.28%)	5 / 81 (6.17%)	
occurrences (all)	14	5	
Thromboembolic event			
Additional description: Thromboembolic event			
subjects affected / exposed	3 / 81 (3.70%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
General disorders and administration site conditions			
Fatigue			
Additional description: Fatigue			
subjects affected / exposed	72 / 81 (88.89%)	53 / 81 (65.43%)	
occurrences (all)	72	53	
Leg oedema			
Additional description: Leg oedema			
subjects affected / exposed	3 / 81 (3.70%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Insomnia			
Additional description: Insomnia			

subjects affected / exposed occurrences (all)	5 / 81 (6.17%) 5	6 / 81 (7.41%) 6	
Pain	Additional description: Pain		
subjects affected / exposed occurrences (all)	44 / 81 (54.32%) 45	49 / 81 (60.49%) 50	
Oedema	Additional description: Oedema		
subjects affected / exposed occurrences (all)	18 / 81 (22.22%) 18	9 / 81 (11.11%) 9	
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 81 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed occurrences (all)	14 / 81 (17.28%) 14	6 / 81 (7.41%) 6	
Cough	Additional description: Cough		
subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 11	4 / 81 (4.94%) 4	
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 81 (0.00%) 0	
Psychiatric disorders			
Hallucinations	Additional description: Hallucinations		
subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	1 / 81 (1.23%) 1	
Injury, poisoning and procedural complications			
Fracture (non-pathological)	Additional description: Fracture (non-pathological)		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 81 (0.00%) 0	
Nervous system disorders			
Dysgeusia	Additional description: Dysgeusia		
subjects affected / exposed occurrences (all)	23 / 81 (28.40%) 23	12 / 81 (14.81%) 12	
Neuropathy	Additional description: Neuropathy		

subjects affected / exposed occurrences (all)	56 / 81 (69.14%) 56	8 / 81 (9.88%) 8	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed occurrences (all)	11 / 81 (13.58%) 11	6 / 81 (7.41%) 6	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed occurrences (all)	18 / 81 (22.22%) 18	1 / 81 (1.23%) 1	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed occurrences (all)	22 / 81 (27.16%) 22	1 / 81 (1.23%) 1	
Ear and labyrinth disorders			
Tinnitus	Additional description: Tinnitus		
subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 8	2 / 81 (2.47%) 2	
Gastrointestinal disorders			
Abdominal distension	Additional description: Abdominal distension		
subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	9 / 81 (11.11%) 9	
Ascites	Additional description: Ascites		
subjects affected / exposed occurrences (all)	10 / 81 (12.35%) 10	2 / 81 (2.47%) 2	
Constipation	Additional description: Constipation		
subjects affected / exposed occurrences (all)	36 / 81 (44.44%) 36	28 / 81 (34.57%) 28	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed occurrences (all)	26 / 81 (32.10%) 26	13 / 81 (16.05%) 13	
Dry mouth	Additional description: Dry mouth		
subjects affected / exposed occurrences (all)	21 / 81 (25.93%) 21	11 / 81 (13.58%) 11	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed occurrences (all)	8 / 81 (9.88%) 8	10 / 81 (12.35%) 10	
Gastrointestinal bleeding	Additional description: Gastrointestinal bleeding		

subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	2 / 81 (2.47%) 2	
Vomiting	Additional description: Vomiting		
subjects affected / exposed occurrences (all)	18 / 81 (22.22%) 18	16 / 81 (19.75%) 16	
Nausea	Additional description: Nausea		
subjects affected / exposed occurrences (all)	41 / 81 (50.62%) 41	32 / 81 (39.51%) 32	
Oral Mucositis	Additional description: Oral Mucositis		
subjects affected / exposed occurrences (all)	30 / 81 (37.04%) 30	4 / 81 (4.94%) 4	
Hepatobiliary disorders			
Biliary event	Additional description: Biliary event		
subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	2 / 81 (2.47%) 2	
Skin and subcutaneous tissue disorders			
Erythema	Additional description: Erythema		
subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	1 / 81 (1.23%) 1	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed occurrences (all)	0 / 81 (0.00%) 0	2 / 81 (2.47%) 2	
Musculoskeletal and connective tissue disorders			
Generalised muscle weakness	Additional description: Generalised muscle weakness		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 81 (1.23%) 1	
Muscle weakness	Additional description: Muscle weakness		
subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6	9 / 81 (11.11%) 9	
Myalgia	Additional description: Myalgia		
subjects affected / exposed occurrences (all)	10 / 81 (12.35%) 10	5 / 81 (6.17%) 6	
Infections and infestations			
Catheter-related infection	Additional description: Catheter-related infection		

subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	0 / 81 (0.00%) 0	
Infection	Additional description: Infection		
subjects affected / exposed occurrences (all)	21 / 81 (25.93%) 21	17 / 81 (20.99%) 17	
Metabolism and nutrition disorders			
Anorexia	Additional description: Anorexia		
subjects affected / exposed occurrences (all)	48 / 81 (59.26%) 48	36 / 81 (44.44%) 37	
Hypercalcemia	Additional description: Hypercalcemia		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	2 / 81 (2.47%) 2	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed occurrences (all)	4 / 81 (4.94%) 4	2 / 81 (2.47%) 2	
Hypophosphatemia	Additional description: Hypophosphatemia		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	1 / 81 (1.23%) 1	
Hyponatremia	Additional description: Hyponatremia		
subjects affected / exposed occurrences (all)	2 / 81 (2.47%) 2	2 / 81 (2.47%) 2	
Hypokalaemia	Additional description: Hypokalaemia		
subjects affected / exposed occurrences (all)	1 / 81 (1.23%) 1	0 / 81 (0.00%) 0	
Hypoalbuminemia	Additional description: Hypoalbuminemia		
subjects affected / exposed occurrences (all)	3 / 81 (3.70%) 3	1 / 81 (1.23%) 1	
Weight loss	Additional description: Weight loss		
subjects affected / exposed occurrences (all)	6 / 81 (7.41%) 6	11 / 81 (13.58%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 October 2013	<p>Update to protocol in line with summary of product characteristics for one of the trial drugs (oxaliplatin). The changes are regarding contraception requirements and the definition of adequate haematological function required to enter the trial. Additionally:</p> <ul style="list-style-type: none"> • Add a further 2 research sites to the trial (centres in Oxford & Belfast) • Correction of an oversight in the patient information sheet, whereby there was no specific mention made of the radioisotope test of kidney function which may be required for some trial patients. • Minor changes to the wording of the patient diary, to ensure clarity and quality of data collected.
01 May 2014	<p>The amendment consists of:</p> <ol style="list-style-type: none"> 1. Amendments to the protocol: <ol style="list-style-type: none"> a. Only excluding patients with previous malignancies if these were within the previous 5 years. b. Allowing the Wright formula to be used as an alternative to the Cockcroft-Gault formula. c. Clarifying that radioisotope determination of GFR in patients with estimated creatinine clearance <math>\leq 30\text{ ml/min}</math> at screening is not mandatory d. Clarifying distribution of consent form copies e. Amendment to suggested premedication guidance relating to ondansetron f. Allowing for local variation in which coagulation tests are completed g. Allowing for pre chemotherapy assessments to be completed within 2 working A Research Ethics Committee established by the Health Research Authority days of treatment h. Other minor clarifications, spelling corrections, correction of contact details. 2. New Participant Information Sheet and informed consent form to be used in the event of a participant's partner becoming pregnant. 3. Two new sites 4. A change of Principal Investigator
18 August 2014	<p>The main purpose of this amendment is to:</p> <p>Make a number of wording changes to the trial protocol. These are fully documented in the enclosed amendment form and amended trial protocol, but in brief they include:</p> <ul style="list-style-type: none"> o Extending the timeline between radiological progression to randomisation to 6 weeks, whilst still ensuring that both randomisation and start of chemotherapy (ARM B ONLY) begin within 6 weeks of progression. o Clarifying that either Alanine Aminotransferase (ALT) and / or Aspartate Aminotransferase (AST) can be performed. o Allowing sites to perform a chest-abdo scan and a pelvic scan separately. o Clarification of the hypertension grading. Patients are only eligible if the hypertension grading is < grade 3 according to CTCAE v4.03, unless controlled with medication and/or diet. o Other minor clarifications, spelling corrections, correction of contact details. <p>Make a number of wording changes to the trial consent form. These are fully documented in the enclosed amendment form and amended informed consent form,</p> <p>but in brief they include:</p> <ul style="list-style-type: none"> o Clarifying that the screening ID must be recorded on the consent form copies as well as the participant ID. o Amendment to the consent form in order to ensure that NHS sites can adhere to the MHRA GCP inspections by ensuring that patients consent for sections of their medical notes and data collected during the study may be looked at by authorised individuals. o Clarification that a copy of the consent form can be provided to the patient rather than the original

11 September 2015	Addition on one study site.
28 October 2015	<ul style="list-style-type: none"> • Reclassifying Calcium Folate and L-Folinic Acid as Non Investigational Medicinal Products (NIMPs) as they were incorrectly classified as Investigational Medicinal Products (IMPs) at set-up. o Change to inclusion criteria 6 to reduce the absolute neutrophil count to reflect the clinical cut-out level for treatment with FOLFOX. o Change to inclusion criteria 12 to clarify wording only. o Change to exclusion criteria 9 to permit patients who do not have a history of other invasive cancers within the last 5 years to enter the trial. • Clarifying platinum sensitivity definitions; a factor controlled for at randomisation: <ul style="list-style-type: none"> o Confirmed 'progressive disease' is 'radiologically confirmed progressive disease'. o Confirmed the three month cut off in days (three months = 90 days) to enable sites to make precise calculations for platinum sensitivity. o Clarified the date of 'completion of last cycle of first line chemotherapy' is defined as the day 1 date of the last cycle given. • Confirming the patient diary at screening must be completed retrospectively for the previous 2 weeks prior to randomisation, if the screening period is over a short time. • Clarifying a 6 week timeframe is allowed from staging CT and optional MR liver scan, to randomisation. • Clarifying baseline and subsequent CT scans must be reported in accordance with RECIST v1.1. • Adding in guidance to ensure translational research samples are not taken from patients with HIV or Hep C or other transmissible human disease; or from patients who are in high risk groups such as intravenous drug users. • Clarifying what needs to be collected when patients are on survival follow-up only. • Clarifying timing for the end of treatment visit (ensuring it is clear this should be carried out within 30 days of the last treatment dose). <p>Changes have also been to the Patient Diary, to make it less onerous to complete and to assist with data interpretation, and to the GP letter as a date field for comp</p>
27 June 2016	<p>Changes made within this amendment are as follows:</p> <ul style="list-style-type: none"> • Change in PI at St James's University Hospital, Leeds. • Change in PI at Nottingham University Hospital, Nottingham (Dr Victoria Brown to Dr Michelle Cunnell) for the period Feb 2016 – Jun 2016 • Change in PI at Nottingham University Hospital, Nottingham (Dr Michelle Cunnell to Dr Arvind Arora) for the period Jun 2016 – present
26 June 2017	<p>Changes made within this amendment are as follows:</p> <p>Removal of Great Western Hospitals NHS Foundation Trust, Swindon Removal of Cheltenham General Hospital Extension to trial end date from 30/04/2017 to 30/11/2018 Change of Principal Investigator at St James Hospital, Leeds Minor clarification added to inclusion criteria 2 – refer to summary of protocol changes document</p>
04 April 2018	<p>This amendment concerns changes to the Reference Safety Information, Section 4.8 Undesirable Effects of Fluorouracil SmPC updated 27-APR-2016 (from version dated 25-MAR-2014) and to the Reference Safety Information, Section 4.8 Undesirable Effects of Oxaliplatin SmPC updated 06-NOV-2016 (from version dated 30-DEC-2013).</p> <p>The Chief Investigator has reviewed the updated SmPCs and confirmed there is no impact to the riskbenefit ratio</p>

03 December 2018	<ul style="list-style-type: none">· All references to the MAHSC-CTU have been updated to the Manchester Clinical Trials Unit (MCTU)· MCTU contact details updated – Project Manager, Statistician and generic e-mail address· Randomisation line details updated· Safety reporting contact details updated
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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/33798493>