# 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 |

### 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 |

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/m^2 5-10 minute bolus (day 1). 2400 mg/m^2 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<br>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<br>Units: Subjects | | | |
| 00 | 28 | 25 | 53 |
| 01 | 52 | 55 | 107 |
| Missing | 1 | 1 | 2 |
| Had previous surgery<br>Units: Subjects | | | |
| Yes | 38 | 34 | 72 |
| No | 43 | 47 | 90 |
| Previous cisplatin and gemcitabine<br>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:<br>Active Symptom Control alone | |
| Reporting group title | ASC plus FOLFOX |
| Reporting group description:<br>Active symptom control plus FOLFOX chemotherapy | |

| Primary: Overall survival | |
|---|---|
| End point title | Overall survival |
| End point description: | |
| End point type | Primary |
| End point timeframe:<br>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 |

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 19.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | ASC plus FOLFOX |
| Reporting group description: - | |
| Reporting group title | ASC alone |

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 | Additional description: Erythema | | |
| 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 | |
| **Renal and urinary disorders** | | | |
| Acute kidney injury | Additional description: Acute kidney injury | | |
| subjects affected / exposed | 3 / 81 (3.70%) | 0 / 81 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | |
| **Musculoskeletal and connective tissue disorders** | | | |
| Rhabdomyolisis | Additional description: Rhabdomyolisis | | |
| 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 / 1 | 0 / 0 | |
| **Infections and infestations** | | | |
| Catheter-related infection | Additional description: Catheter-related infection | | |
| 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 | |
| Infection | Additional description: Infection | | |
| subjects affected / exposed | 13 / 81 (16.05%) | 5 / 81 (6.17%) | |
| occurrences causally related to treatment / all | 8 / 13 | 0 / 5 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 2 | |
| **Metabolism and nutrition disorders** | | | |
| Diabetic ketoacidosis | Additional description: Diabetic ketoacidosis | | |
| 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 / 1 | 0 / 0 | |
| Dehydration | Additional description: Dehydration | | |
| 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 | |
| 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 | 5 / 81 (6.17%) | 6 / 81 (7.41%) | |
| occurrences (all) | 5 | 6 | |
| Pain | Additional description: Pain | | |
| subjects affected / exposed | 44 / 81 (54.32%) | 49 / 81 (60.49%) | |
| occurrences (all) | 45 | 50 | |
| Oedema | Additional description: Oedema | | |
| subjects affected / exposed | 18 / 81 (22.22%) | 9 / 81 (11.11%) | |
| occurrences (all) | 18 | 9 | |
| **Immune system disorders** | | | |
| Allergic reaction | Additional description: Allergic reaction | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 81 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| **Respiratory, thoracic and mediastinal disorders** | | | |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 14 / 81 (17.28%) | 6 / 81 (7.41%) | |
| occurrences (all) | 14 | 6 | |
| Cough | Additional description: Cough | | |
| subjects affected / exposed | 11 / 81 (13.58%) | 4 / 81 (4.94%) | |
| occurrences (all) | 11 | 4 | |
| Hypoxia | Additional description: Hypoxia | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 81 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| **Psychiatric disorders** | | | |
| Hallucinations | Additional description: Hallucinations | | |
| subjects affected / exposed | 0 / 81 (0.00%) | 1 / 81 (1.23%) | |
| occurrences (all) | 0 | 1 | |
| **Injury, poisoning and procedural complications** | | | |
| Fracture (non-pathological) | Additional description: Fracture (non-pathological) | | |
| subjects affected / exposed | 1 / 81 (1.23%) | 0 / 81 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| **Nervous system disorders** | | | |
| Dysgeusia | Additional description: Dysgeusia | | |
| subjects affected / exposed | 23 / 81 (28.40%) | 12 / 81 (14.81%) | |
| occurrences (all) | 23 | 12 | |
| Neuropathy | Additional description: Neuropathy | | |

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

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

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

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 18 October 2013 | 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.<br>Additionally:<br>• Add a further 2 research sites to the trial (centres in Oxford & Belfast)<br>• 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.<br>• Minor changes to the wording of the patient diary, to ensure clarity and quality of data collected. |
| 01 May 2014 | The amendment consists of:<br>1. Amendments to the protocol:<br>a. Only excluding patients with previous malignancies if these were within the previous 5 years.<br>b. Allowing the Wright formula to be used as an alternative to the Cockroft-Gault formula.<br>c. Clarifying that radioisotope determination of GFR in patients with estimated creatinine clearance <30 ml/min at screening is not mandatory<br>d. Clarifying distribution of consent form copies<br>e. Amendment to suggested premedication guidance relating to ondansetron<br>f. Allowing for local variation in which coagulation tests are completed<br>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<br>h. Other minor clarifications, spelling corrections, correction of contact details.<br>2. New Participant Information Sheet and informed consent form to be used in the event of a participant's partner becoming pregnant.<br>3. Two new sites<br>4. A change of Principal Investigator |
| 18 August 2014 | The main purpose of this amendment is to:<br>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:<br>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.<br>o Clarifying that either Alanine Aminotransferase (ALT) and / or Aspartate Aminotransferase (AST) can be performed.<br>o Allowing sites to perform a chest-abdo scan and a pelvic scan separately.<br>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.<br>o Other minor clarifications, spelling corrections, correction of contact details.<br>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,<br>but in brief they include:<br>o Clarifying that the screening ID must be recorded on the consent form copies as well as the participant ID.<br>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.<br>o Clarification that a copy of the consent form can be provided to the patient rather than the original |

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|---|---|
| 11 September 2015 | Addition on one study site. |
| 28 October 2015 | • Reclassifying Calcium Folinate and L-Folinic Acid as Non Investigational Medicinal Products (NIMPs) as they were incorrectly classified as Investigational Medicinal Products (IMPs) at set-up.<br>o Change to inclusion criteria 6 to reduce the absolute neutrophil count to reflect the clinical cut-out level for treatment with FOLFOX.<br>o Change to inclusion criteria 12 to clarify wording only.<br>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.<br>• Clarifying platinum sensitivity definitions; a factor controlled for at randomisation:<br>o Confirmed 'progressive disease' is 'radiologically confirmed progressive disease'.<br>o Confirmed the three month cut off in days (three months = 90 days) to enable sites to make precise calculations for platinum sensitivity.<br>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.<br>• 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.<br>• Clarifying a 6 week timeframe is allowed from staging CT and optional MR liver scan, to randomisation.<br>• Clarifying baseline and subsequent CT scans must be reported in accordance with RECIST v1.1.<br>• 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.<br>• Clarifying what needs to be collected when patients are on survival follow-up only.<br>• 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).<br><br>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 |
| 27 June 2016 | Changes made within this amendment are as follows:<br><br>• Change in PI at St James's University Hospital, Leeds.<br>• Change in PI at Nottingham University Hospital, Nottingham (Dr Victoria Brown to Dr Michelle Cunnell) for the period Feb 2016 – Jun 2016<br>• Change in PI at Nottingham University Hospital, Nottingham (Dr Michelle Cunnell to Dr Arvind Arora) for the period Jun 2016 – present |
| 26 June 2017 | Changes made within this amendment are as follows:<br>Removal of Great Western Hospitals NHS Foundation Trust, Swindon<br>Removal of Cheltenham General Hospital<br>Extension to trial end date from 30/04/2017 to 30/11/2018<br>Change of Principal Investigator at St James Hospital, Leeds<br>Minor clarification added to inclusion criteria 2 – refer to summary of protocol changes<br>document |
| 04 April 2018 | This amendment concerns changes to the Reference Safety Information, Section 4.8 Undesirable<br>Effects of Fluorouracil SmPC updated 27-APR-2016 (from version dated 25-MAR-2014) and to the<br>Reference Safety Information, Section 4.8 Undesirable Effects of Oxaliplatin SmPC updated 06-NOV-<br>2016 (from version dated 30-DEC-2013).<br>The Chief Investigator has reviewed the updated SmPCs and confirmed there is no impact to the riskbenefit<br>ratio |

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| 03 December 2018 | · All references to the MAHSC-CTU have been updated to the Manchester Clinical Trials Unit (MCTU)<br>· MCTU contact details updated – Project Manager, Statistician and generic e-mail address<br>· Randomisation line details updated<br>· Safety reporting contact details updated |

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