# Clinical trial results:
# A multi-centre phase II trial to assess the efficacy of epirubicin, cisplatin and capecitabine incorporating the prospective validation of molecular classifiers and exploratory metabonomics.

## Summary

| | |
|---|---|
| EudraCT number | 2008-000657-35 |
| Trial protocol | GB |
| Global end of trial date | 30 November 2016 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 04 August 2019 |
| First version publication date | 04 August 2019 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CUP ONE |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | ISRCTN17282276 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | University of Glasgow |
| Sponsor organisation address | University Avenue, Glasgow, United Kingdom, G12 8QQ |
| Public contact | Dr Debra Stuart, University of Glasgow, 0044 0141 330 4539, debra.stuart@glasgow.ac.uk |
| Scientific contact | Dr Debra Stuart, University of Glasgow, 0044 0141 330 4539, debra.stuart@glasgow.ac.uk |
| Sponsor organisation name | NHS Greater Glasgow and Clyde |
| Sponsor organisation address | Dykebar Hospital, Grahamston Road, Paisley, United Kingdom, PA2 7DE |
| Public contact | Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0044 0141 314 4712, margaret.fegen@ggc.scot.nhs.uk |
| Scientific contact | Dr Margaret Fegen, NHS Greater Glasgow and Clyde, 0044 0141 314 4172, margaret.fegen@ggc.scot.nhs.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 | 12 June 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 November 2016 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Translational: To select the molecular classifier with the highest diagnostic accuracy

Clinical Trial: To estimate the response rate from the ECX regimen

Protection of trial subjects:

The treatment being received in the context of the clinical trial is same treatment patients would have received in standard of care if they had not entered the trial.
The treatment and number and type of investigations involved were fully explained to patients verbally and in writing via the patient information sheet to ensure patients were fully aware what was entailed in participating in the trial prior to the consenting to the study.

The patient information sheet also fully explained the aims of the study.
The side effects of the drugs epirubicin, cisplatin and capecitabine being given were explained in patient information sheet, as where the expected side effects. All patients were closely monitored throughout the course of the study for adverse events and were advised to report adverse events to their study team as they arose.

With measures included in the protocol for management of adverse events.

Background therapy:

-

Evidence for comparator:

No comparator. The study was multicentre non-randomised non-controlled exploratory phase II trial

| | |
|---|---|
| Actual start date of recruitment | 01 February 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | United Kingdom: 59 |
| Worldwide total number of subjects | 59 |
| EEA total number of subjects | 59 |

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) | 34 |
| From 65 to 84 years | 25 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study opened to recruitment in February 2010 and closed to recruitment in November 2014 . This study was opened to recruitment in the United Kingdom only.

### Pre-assignment

Screening details:

The screening period for the trial was up to 28 days prior to registration. Prior to screening investigations commencing patient must have provided informed consent to participate in the study.

### Period 1

| | |
|---|---|
| Period 1 title | Overall Trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| | |
|---|---|
| **Arm title** | ECX Chemotherapy |

Arm description:

Combination chemotherapy: epirubicin (E), cisplatin (C) and capecitabine (X)

| | |
|---|---|
| Arm type | Single |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Patients receive Cisplatin 60mg/m2 once every 3 weeks (maximum 8 cycles)

| | |
|---|---|
| Investigational medicinal product name | Epirubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

Epirubicin 50mg/m2 IV bolus once every 3 weeks (maximum 8 cycles)

| | |
|---|---|
| Investigational medicinal product name | Capecitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Capecitabine 1000mg/m2 daily in 2 divided dose for 24 weeks.

| **Number of subjects in period 1** | ECX Chemotherapy |
|---|---|
| Started | 59 |
| Completed | 59 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Overall Trial |
|---|---|

Reporting group description: -

| Reporting group values | Overall Trial | Total | |
|---|---|---|---|
| Number of subjects | 59 | 59 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | | 0 | |
| Newborns (0-27 days) | | 0 | |
| Infants and toddlers (28 days-23 months) | | 0 | |
| Children (2-11 years) | | 0 | |
| Adolescents (12-17 years) | | 0 | |
| Adults (18-64 years) | | 0 | |
| From 65-84 years | | 0 | |
| 85 years and over | | 0 | |
| Age continuous | | | |
| Age at registration | | | |
| Units: years | | | |
| median | 63 | | |
| inter-quartile range (Q1-Q3) | 50 to 68 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 31 | 31 | |
| Male | 28 | 28 | |
| ECOG Performance Status<br>Units: Subjects | | | |
| ECOG 0 | 23 | 23 | |
| ECOG 1 | 36 | 36 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | ECX Chemotherapy |
| Reporting group description: | |
| Combination chemotherapy: epirubicin (E), cisplatin (C) and capecitabine (X) | |
| Subject analysis set title | ITT Population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: | |
| All patients registered on to the clinical trial | |
| Subject analysis set title | Main Study Analysis for Primary Analysis |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| ITT population excluding patients with gross eligibility deviations or lack of measurable disease at baseline | |
| Subject analysis set title | Main Study Analysis for Secondary Analysis |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| ITT population excluding patients with gross eligibility deviations | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: | |
| Patients starting ECX treatment | |

### Primary: RECIST Response Rate

| | |
|---|---|
| End point title | RECIST Response Rate |
| End point description: | |
| Best overall response (complete response or partial response) recorded for a patient over the course of chemotherapy as assessed using RECIST guidelines (see Appendix V of the study protocol). | |
| End point type | Primary |
| End point timeframe: | |
| Best response rate during chemotherapy (up to 8 cycles) | |

| End point values | ECX Chemotherapy | Main Study Analysis for Primary Analysis | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 55 | 55 | | |
| Units: Patients | | | | |
| Responders | 17 | 17 | | |
| Non-responders | 34 | 34 | | |
| Unevaluable | 4 | 4 | | |

## Statistical analyses

| **Statistical analysis title** | RECIST Response Rate |
|---|---|
| Comparison groups | ECX Chemotherapy v Main Study Analysis for Primary Analysis |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | other[1] |
| Parameter estimate | Proportion |
| Point estimate | 0.309 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.218 |
| upper limit | 0.419 |

Notes:

[1] - The study design required 17 responses out of 57 evaluable patients in order to achieve 95% power, a proportion of 0.298. In addition to the analysis planned in the SAP, we made an adjustment for the study under-running and not obtaining the required 57 patients (Koyama T, Chen H. Proper inference from Simon's two-stage designs. Stat Med. 2008;27(16):3145–54. doi: 10.1002/sim.3123. View ArticlePubMedGoogle Scholar). The result was positive for both analyses.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were reported up to 30 days after the administration of the last trial treatment. Any suspected SAR or medically significant SAE that occurred 30 days post treatment (with no time limit) was also reported

| | |
|---|---|
| Assessment type | Systematic |

### Dictionary used

| | |
|---|---|
| Dictionary name | CTCAE |
| Dictionary version | 3.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Safety Population |

Reporting group description: -

| Serious adverse events | Safety Population | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 39 / 57 (68.42%) | | |
| number of deaths (all causes) | 49 | | |
| number of deaths resulting from adverse events | 4 | | |
| Vascular disorders | | | |
| Thrombosis | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutrophils | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences causally related to treatment / all | 5 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Edema - Limb | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences causally related to treatment / all | 3 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 6 / 57 (10.53%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Fever | | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Death not associated with CTCAE term | | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 1 / 4 | | | |
| Gastrointestinal disorders | | | | |
| Ascites | | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 6 / 57 (10.53%) | | | |
| occurrences causally related to treatment / all | 5 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nausea | | | | |
| subjects affected / exposed | 7 / 57 (12.28%) | | | |
| occurrences causally related to treatment / all | 8 / 8 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 9 / 57 (15.79%) | | | |
| occurrences causally related to treatment / all | 8 / 9 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pain - Abdomen | | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | | |
| occurrences causally related to treatment / all | 1 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infections and infestations | | | | |

| | | | |
|---|---|---|---|
| Infection - Other | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences causally related to treatment / all | 2 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences causally related to treatment / all | 1 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| **Non-serious adverse events** | Safety Population | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 57 / 57 (100.00%) | | |
| Investigations | | | |
| Weight loss | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences (all) | 7 | | |
| Nervous system disorders | | | |
| Motor neoropathy | | | |
| subjects affected / exposed | 7 / 57 (12.28%) | | |
| occurrences (all) | 15 | | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 57 (10.53%) | | |
| occurrences (all) | 8 | | |
| Blood and lymphatic system disorders | | | |
| Other blood and lymphatic system disorder | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Edema - Limb | | | |
| subjects affected / exposed | 13 / 57 (22.81%) | | |
| occurrences (all) | 31 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 7 / 57 (12.28%) | | |
| occurrences (all) | 10 | | |
| White blood cell count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 11 / 57 (19.30%) | | |
| occurrences (all) | 23 | | |
| General disorders and administration site conditions | | | |
| Other general disorder and administration site condition | | | |
| subjects affected / exposed | 5 / 57 (8.77%) | | |
| occurrences (all) | 6 | | |
| Lethargy | | | |
| subjects affected / exposed | 54 / 57 (94.74%) | | |
| occurrences (all) | 213 | | |
| Pain | | | |
| subjects affected / exposed | 38 / 57 (66.67%) | | |
| occurrences (all) | 111 | | |
| Fatigue | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 7 | | |
| Ear and labyrinth disorders | | | |
| Tinnitus | | | |
| subjects affected / exposed | 29 / 57 (50.88%) | | |
| occurrences (all) | 46 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 4 | | |
| Gastrointestinal disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 6 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 4 / 57 (7.02%) | | |
| occurrences (all) | 5 | | |
| Mucositis oral | | | |
| subjects affected / exposed | 3 / 57 (5.26%) | | |
| occurrences (all) | 3 | | |
| Stomatitis | | | |
| subjects affected / exposed | 29 / 57 (50.88%) | | |
| occurrences (all) | 46 | | |

| | | | |
|---|---|---|---|
| Anorexia<br>subjects affected / exposed<br>occurrences (all) | 18 / 57 (31.58%)<br>50 | | |
| Constipation<br>subjects affected / exposed<br>occurrences (all) | 36 / 57 (63.16%)<br>83 | | |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 26 / 57 (45.61%)<br>61 | | |
| Nausea<br>subjects affected / exposed<br>occurrences (all) | 41 / 57 (71.93%)<br>116 | | |
| Vomiting<br>subjects affected / exposed<br>occurrences (all) | 30 / 57 (52.63%)<br>69 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Other respiratory, thoracic and mediastinal disorder<br>subjects affected / exposed<br>occurrences (all) | 5 / 57 (8.77%)<br>5 | | |
| Sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 17 / 57 (29.82%)<br>61 | | |
| Cough<br>subjects affected / exposed<br>occurrences (all) | 7 / 57 (12.28%)<br>11 | | |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 6 / 57 (10.53%)<br>10 | | |
| Skin and subcutaneous tissue disorders | | | |
| Hand foot skin reaction<br>subjects affected / exposed<br>occurrences (all) | 19 / 57 (33.33%)<br>46 | | |
| Other skin and subcutaneous disorder<br>subjects affected / exposed<br>occurrences (all) | 3 / 57 (5.26%)<br>6 | | |

| | | | |
|---|---|---|---|
| Alopecia<br>subjects affected / exposed<br>occurrences (all) | 51 / 57 (89.47%)<br>203 | | |
| Psychiatric disorders<br>Insomnia<br>subjects affected / exposed<br>occurrences (all) | 3 / 57 (5.26%)<br>9 | | |
| Infections and infestations<br>Other infection and infestation<br>subjects affected / exposed<br>occurrences (all) | 6 / 57 (10.53%)<br>9 | | |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

| |
|---|
| None reported |

Notes: