



## 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
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#### 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
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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:

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## 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:

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## 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

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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 were 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:

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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:

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## 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:

<b>Subjects enrolled per age group</b>	
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
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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/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> daily in 2 divided dose for 24 weeks.

<b>Number of subjects in period 1</b>	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			
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			
Units: Subjects			
Female	31	31	
Male	28	28	
ECOG Performance Status			
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

<b>Statistical analysis title</b>	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 <sup>[1]</sup>
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
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

### Reporting groups

Reporting group title	Safety Population
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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 %

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

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

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### 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
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Notes: