

# The efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary origin (CUP): prospective validation of diagnosis, classification and metabolic responses

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<b>Registration date</b> 02/02/2011	<b>Overall study status</b> Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 14/10/2020	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## Plain English summary of protocol

<http://cancerhelp.cancerresearchuk.org/trials/a-trial-of-chemotherapy-cancer-unknown-primary-cup-one>

## Contact information

### Type(s)

Scientific

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## Additional identifiers

### Clinical Trials Information System (CTIS)

2008-000657-35

### Protocol serial number

MI67

# Study information

## Scientific Title

A multicentre phase II trial to assess the efficacy of epirubicin, cisplatin and capecitabine in carcinomas of unknown primary origin (CUP): incorporating the prospective validation of molecular classifiers in diagnosis and classification and exploratory metabonomics

## Acronym

CUP ONE

## Study objectives

Carcinomas of unknown primary origin (CUP) constitute 3 - 10% of all cancer diagnosis, and ranks among the top ten commonest malignancies. The prognosis of these patients is poor, with a median survival of 8 - 12 months from diagnosis. Post-mortem analysis of CUP patients suggest that the commonest primaries found are in the pancreas and lung (accounting for 40%).

There are few clinical treatment studies of CUP, and therefore no consensus on treatment standards. Epirubicin, cisplatin and 5-fluorouracil (ECF) chemotherapy regimen is commonly used in CUP, due to its broad spectrum activity against a variety of known primary cancers, including pancreas, lung and other gastro-intestinal (GI) cancers. Epirubicin, cisplatin and capecitabine (ECX) regimen has recently been confirmed as an equivalent alternative to ECF in gastro-oesophageal cancers. It is superior in terms of tolerability and treatment related complications.

A large variety of cancers have abnormalities, including overexpression, of molecular pathways involved in promoting abnormal cell growth and metastasis, such as the epidermal growth factor receptors (EGFR) and the vascular endothelial growth factor (VEGF). Inhibitors of EGFR activity, for example, have over the last two years shown clinical efficacy and survival benefits in pancreatic, lung, breast and head and neck cancers in particular. These have yet to be systematically investigated in CUP. These signalling pathways may be potentially critical in CUP, as many cases are thought to have a primary originating in the pancreas, lung or GI tract. The EGFR pathway is also dysregulated in studies of CUP tissue.

CUP is a neglected research entity despite its relative frequency. As it presents with metastasis by definition, it is distinguished by its aggressive progression. Further studies are therefore necessary to study the biology of these heterogeneous cancers. This study allows for multiple translational components to be established. Tissues from CUP biopsies will be used to identify molecular characteristics and so the potential sites of the primary cancer, as well as in the analysis of the distinguishing biological nature of these cancers. The laboratory component will incorporate three methods for site of origin classification including two mRNA transcriptional profiling methods, using either microarray (expression profiling discovery microarrays) or real-time polymerase chain reaction (RT-PCR) in addition to one immunohistochemistry based analysis; and metabonomic analysis of blood and urine (exploratory analysis).

## Ethics approval required

Old ethics approval format

## Ethics approval(s)

Riverside Research Ethics Committee, 08/10/2008, ref: 08/H0706/61

## Study design

Multicentre non-randomised non-controlled exploratory phase II trial

## **Primary study design**

Interventional

## **Study type(s)**

Treatment

## **Health condition(s) or problem(s) studied**

Carcinoma of unknown primary origin (CUP)

## **Interventions**

Treatment will be planned for 8 cycles over 24 weeks with radiological assessments at 12 weeks and 24 weeks or if clinically indicated. Patients progressing or intolerant of trial therapy will discontinue study treatment. Second-line therapy may be offered but is not mandated in this study.

1. Epirubicin: 50 mg/m<sup>2</sup> intravenous (IV) bolus once every 3 weeks (maximum 8 cycles)
2. Cisplatin: 60 mg/m<sup>2</sup> with hydration (see below) once every 3 weeks (maximum 8 cycles)
3. Capecitabine: 1000 mg/m<sup>2</sup> daily in 2 divided doses for 24 weeks

## **Intervention Type**

Drug

## **Phase**

Not Applicable

## **Drug/device/biological/vaccine name(s)**

Epirubicin, cisplatin, capecitabine

## **Primary outcome(s)**

1. Translational: To select the molecular classifier with the highest diagnostic accuracy
2. Clinical Trial: To estimate the response rate from the ECX regimen

Outcomes measured retrospectively. There is an efficacy analysis of response when 24 patients are recruited to Clinical Trial (Part 2 of the study).

## **Key secondary outcome(s)**

Clinical Trial:

1. Progression-free survival
2. Overall survival
3. Quality of life analysis
4. Cost-utility comparison of diagnostic molecular classifiers with average clinical diagnostic work-up
5. Correlation of molecular profiles with patient outcome
6. Identification of potential prognostic metabonomic signatures to efficacy and toxicity profiles

Outcomes measured retrospectively. There is an efficacy analysis of response when 24 patients are recruited to Clinical Trial (Part 2 of the study).

## **Completion date**

## Eligibility

### Key inclusion criteria

Translational Registration (part 1):

1. Uncertain or unknown primary site of origin of malignancy. This includes patients with a suspected primary site (on history, histology or radiology) but as yet unconfirmed.
2. Histologically confirmed carcinomas (adenocarcinomas, squamous cell carcinoma [SCC] and undifferentiated are all acceptable) from tru-cut biopsy and/or operative procedure
3. Lymphomas, sarcomas, germ-cell tumours are not intended to be either part of this trial, if uncertain or equivocal they can be discussed with the Trial Management Group (TMG)
4. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can only be offered the translational part of the study if either a subsequent tru-cut biopsy, or an operative procedure is to be performed at some stage of the patients investigations or surgical treatment (such as debulking or bypass surgery)
5. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can however still be offered the clinical part of the study
6. Written informed consent is required for both parts separately

Clinical Trial Registration for ECX treatment (part 2):

1. Histologically or cytologically confirmed carcinomas, in which a primary cannot be conclusively identified following appropriate investigations and discussion in the appropriate MDM:
  - 1.1. Lymphomas, sarcomas and germ-cell tumours are not intended to be part of this trial, if uncertain or equivocal they can be discussed with the TMG
  - 1.2. Cytologically confirmed carcinomas, in which a primary cannot be found following appropriate investigations, can be offered both parts of the study only if either a subsequent tru-cut biopsy and/or operative procedure is to be performed at some stage of the patient's investigations or surgical treatment (such as debulking or bypass surgery). Written informed consent is required for both parts separately.
  - 1.3. If only cytological confirmation from a FNA is possible, only the second part of the study can be considered
2. Inoperable metastatic carcinoma with at least unidimensional measurable disease
3. Aged less than 18 years
4. Performance status less than 2
5. Life expectancy greater than 12 weeks
6. Adequate haematological function: absolute neutrophil count less than  $2.0 \times 10^9/l$ , white cell count less than  $3.0 \times 10^9/l$ , platelets less than  $100 \times 10^9/l$
7. Adequate calculated or measured renal function: serum creatinine less than 120 mg/dl and creatinine clearance greater than 60 ml/min (renal function assessed by either 24 hour creatinine or EDTA clearance, is often more accurate than calculated clearances which can underestimate the true clearance)
8. Adequate hepatic function: bilirubin within 2 x normal range, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than or equal to 5 times the upper limit of normal
9. Written informed consent

### Participant type(s)

Patient

Healthy volunteers allowed

No

**Age group**

Adult

**Lower age limit**

18 years

**Sex**

All

**Total final enrolment**

59

**Key exclusion criteria**

Translational Registration (part 1):

1. Significant intercurrent medical or psychiatric illness which in the opinion of the investigator would compromise the patient's ability to give informed consent
2. Non-carcinoma histology (lymphomas, sarcomas and germ-cell tumours are not intended to be part of this trial; if equivocal discuss with TMG)

Clinical Trial Registration for ECX treatment (part 2):

1. Previous chemotherapy
2. Co-existent second malignancy or history of prior malignancy within 5 years, except for adequately treated basal cell carcinoma and non-invasive carcinoma of the cervix. If history of prior malignancy within 10 years, the previous histology should be compared and available for central review.
3. Pregnant or lactating women. Women of child bearing potential not prepared to use effective contraception.
4. Significant intercurrent medical or psychiatric illness which in the opinion of the investigator would compromise the patient's ability to give informed consent or tolerate the therapy
5. Uncontrolled angina pectoris, heart failure, clinically significant uncontrolled cardiac arrhythmias, or any patient with a clinically significant abnormal electrocardiogram (ECG) or cardiac history having a left ventricular ejection fraction (LVEF) of lower limit of normal range for institution as determined by multiple gated acquisition (MUGA) scan or echocardiogram
6. The presence of proven cerebral metastases
7. Any chemotherapy, hormonal or immunotherapy or other investigational drug within the preceding 4 weeks (steroids are permissible)
8. Previous radiotherapy is allowed but not to sites of assessable disease. No chemotherapy is to be given until resolution of all acute radiotherapy effects or a minimum of 6 weeks has elapsed since end of radiotherapy. Radiosensitisation with chemotherapy during radiotherapy is not allowed.
9. Hearing difficulties which in the investigators opinion, might significantly worsen with cisplatin therapy

**Date of first enrolment**

30/04/2010

**Date of final enrolment**

30/10/2013

# Locations

## Countries of recruitment

United Kingdom

England

## Study participating centre

Hammersmith Hospital

London

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# Sponsor information

## Organisation

NHS Greater Glasgow and Clyde (UK)

## ROR

<https://ror.org/05kdz4d87>

# Funder(s)

## Funder type

Charity

## Funder Name

Cancer Research UK (CRUK) (UK) - Clinical Trials Advisory and Awards Committee (CTAAC) and Translational Research in Clinical Trials Committee (TRICC) grant awards

# Results and Publications

## Individual participant data (IPD) sharing plan

## IPD sharing plan summary

Not provided at time of registration

## Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
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<a href="#">Basic results</a>			28/05/2020	No	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Participant information sheet</a>	Participant information sheet	11/11/2025	11/11/2025	No	Yes
<a href="#">Plain English results</a>			14/10/2020	No	Yes