

# A randomised phase II/III trial of peri-operative chemotherapy with or without bevacizumab in operable adenocarcinoma of the stomach and gastro-oesophageal junction

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|----------------------------------------|---------------------------------------------------|---------------------------------------------------------------------------------------------------|
| <b>Submission date</b><br>07/11/2006   | <b>Recruitment status</b><br>No longer recruiting | <input type="checkbox"/> Prospectively registered<br><input type="checkbox"/> Protocol            |
| <b>Registration date</b><br>25/01/2007 | <b>Overall study status</b><br>Completed          | <input type="checkbox"/> Statistical analysis plan<br><input checked="" type="checkbox"/> Results |
| <b>Last Edited</b><br>24/09/2020       | <b>Condition category</b><br>Cancer               | <input type="checkbox"/> Individual participant data                                              |

## Plain English summary of protocol

<http://www.cancerhelp.org.uk/trials/a-trial-comparing-chemotherapy-and-bevacizumab-with-chemotherapy-alone-for-cancer-of-the-stomach-or-the-junction-of-the-stomach-and-oesophagus>

## Contact information

### Type(s)

Scientific

### Contact name

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## Additional identifiers

ClinicalTrials.gov (NCT)

NCT00450203

## Clinical Trials Information System (CTIS)

2006-000811-12

### Protocol serial number

MRC CTU ST03

## Study information

### Scientific Title

A randomised phase II/III trial of peri-operative chemotherapy with or without bevacizumab in operable adenocarcinoma of the stomach and gastro-oesophageal junction

### Study objectives

Does the addition of bevacizumab to standard chemotherapy: Epirubicin, Cisplatin, Capecitabine (ECX) improve overall survival?

### Ethics approval required

Old ethics approval format

### Ethics approval(s)

Sunderland Research Ethics Committee, ref: 06/Q0904/78

### Primary study design

Interventional

### Study design

Open-label randomised controlled phase II/III clinical trial

### Study type(s)

Treatment

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

Cancer of the stomach and gastro-oesophageal junction adenocarcinoma

### Interventions

Patients will be randomised to receive:

1. Six cycles of peri-operative ECX chemotherapy alone
2. Six cycles of peri-operative ECX chemotherapy with Bevacizumab

Plus an additional six cycles of Bevacizumab as maintenance therapy after post-operative chemotherapy in 1:1 ratio.

Control Arm ECX:

Patients randomised to the control arm (ECX) will receive three cycles of ECX chemotherapy:

1. Epirubicin 50 mg/m<sup>2</sup> Intravenous [IV] day one
2. Cisplatin 60 mg/m<sup>2</sup> IV day one
3. Capecitabine 1250 mg/m<sup>2</sup> orally (po) daily in two divided doses day one to 21 pre-operatively)

Surgery will be performed as detailed in the protocol, followed by three post-operative cycles of ECX at the same doses as above. Pre-operative chemotherapy is expected to take nine weeks and surgery should take place five to six weeks after this. Post-operative chemotherapy should recommence six to ten weeks after surgery and should last for another nine weeks. Therefore the duration of treatment in the control arm is expected to be 30 to 34 weeks.

#### **Investigational Arm ECX + B:**

Patients randomised to the investigational arm (ECX + B) will receive treatment as specified above but in addition on day one of every cycle of chemotherapy they will receive bevacizumab 7.5 mg/kg IV. In addition once the three cycles of post-operative chemotherapy are completed they will receive six doses of maintenance bevacizumab 7.5 mg/kg IV once every 21 days.

For the investigational arm treatment intervals will be the same. The five to six week interval between the last Capecitabine tablet and surgery will also ensure that patients have at least an eight week break between the last pre-operative injection of bevacizumab given at the beginning of the third cycle and their surgery, to minimise the risk of bevacizumab related peri-operative morbidity. Postoperative chemotherapy should recommence six to ten weeks after surgery and should last for another nine weeks. This is standard practice for the use of peri-operative chemotherapy in patients receiving gastrectomies. Patients in this arm will also receive six bevacizumab maintenance injections of bevacizumab lasting 18 weeks so that the total duration of therapy on the investigational arm will be 52 weeks.

#### **Intervention Type**

Drug

#### **Phase**

Phase II/III

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

Bevacizumab, Epirubicin, Cisplatin, Capecitabine

#### **Primary outcome(s)**

1. Safety, assessed by monitoring gastric perforations, cardiac toxicity, wound healing complications, GastroIntestinal (GI) bleeding and perforations
2. Overall survival

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

1. Treatment-related morbidity
2. Response rates to pre-operative treatment
3. Surgical resection rates
4. Disease-free survival
5. Quality of life
6. Cost-effectiveness

#### **Completion date**

31/10/2012

## **Eligibility**

#### **Key inclusion criteria**

1. Patients with histologically verified gastric or type III gastro-oesophageal junction adenocarcinoma, who have not received any treatment for their cancer
2. Tumours should be stage 1b (T1 N1), II, III with no evidence of distant metastases or stage IV considered to be T4, N1 or N2, M0 where the surgeon believes that an R0 resection can be achieved by excision of a contiguous structure. All patients should have a laparoscopy and a Computed Tomography (CT) of chest and abdomen (pelvis is optional) prior to study entry. Endoscopic UltraSound (EUS) should be performed for all type III gastro-oesophageal junctional tumours and according to local practice for other tumours

Assessments to be performed within four weeks prior to randomisation:

1. World Health Organisation (WHO) performance status zero or one
2. Adequate respiratory function: Forced Expiratory Volume in one second (FEV1) more than 1.5 litres
3. Adequate cardiac ejection fraction more than 50% (as determined by Multiple Gated Acquisition scan [MUGA] or Echocardiogram [ECHO])

Assessments to be performed within one week prior to randomisation:

1. Adequate bone marrow function:
  - 1.1. Absolute Neutrophil Count (ANC) more than 1.5 litres
  - 1.2. white blood cell count more than  $3 \times 10^9/l$
  - 1.3. platelets more than  $100 \times 10^9/l$
  - 1.4. Haemoglobin (Hb) more than 9 g/dl (can be post-transfusion)
2. Adequate renal function: glomerular filtration rate more than 60 ml/minute (calculated or measured)
3. Adequate liver function:
  - 3.1. serum bilirubin 1.5 x Upper Limit of Normal (ULN)
  - 3.2. Alanine Aminotransferase (ALT)/Aspartate Aminotransferase (AST) less than or equal to 2.5 x ULN
  - 3.3. Alkaline Phosphatase (ALP) less than or equal to 3 x ULN (in the absence of liver metastases)
4. Proteinuria at baseline less than 1 g of protein/24 hours by a 24-hour urine collection
5. Adequate coagulation profile:
  - 5.1. International Normalised Ratio (INR) less than 1.5 x ULN
  - 5.2. Activated Partial Thromboplastin Time (APTT) less than 1.5 x ULN
6. Patients on oral anticoagulation must change to lower molecular weight heparin prior to randomisation, to be eligible
7. Patient is fit to receive all protocol treatment
8. Completion of baseline quality of life questionnaire
9. No other malignancies within the last four years (other than curatively treated basal cell carcinoma of the skin and/or in situ carcinoma of the cervix)
10. Women of childbearing potential should have a negative pregnancy test within seven days prior to commencing treatment, or have amenorrhoea for more than two years. Fertile men and women must agree to take adequate contraceptive precautions

### **Participant type(s)**

Patient

### **Healthy volunteers allowed**

No

### **Age group**

Adult

**Sex**

All

**Key exclusion criteria**

Significant co-existing or previous medical conditions:

1. Cerebrovascular disease (including Transient Ischaemic Attacks [TIA] and strokes) within a year before trial entry
2. Cardiovascular diseases as follows:
  - 2.1. Myocardial infarction (less than one year prior to randomisation)
  - 2.2. Uncontrolled hypertension while receiving chronic medication
  - 2.3. Unstable angina
  - 2.4. New York Heart Association (NYHA) grade II or greater congestive heart failure
  - 2.5. Serious cardiac arrhythmia requiring medication
3. Major surgery, major trauma or open biopsy within 28 days prior to study entry
4. Serious non-healing wound, ulcer or bone fracture
5. Evidence of bleeding diathesis or coagulopathy
6. Recent history of any active gastrointestinal inflammatory condition such as peptic ulcer disease. If patients have a known diagnosis of any of the above, evidence of disease control is required negative endoscopy within the past 28 days

Other exclusion factors:

1. Patients with clinically apparent hearing impairment and tinnitus
2. Lack of physical integrity of the upper gastro-intestinal tract, malabsorption syndrome, or inability to take oral medication
3. Patients requiring ongoing treatment with contraindicated concomitant medication
4. Patients who have previously received anthracycline treatment
5. Known peripheral neuropathy greater than or equal to grade one (absence of deep tendon reflexes as the sole neurological abnormality does not render the patient ineligible)
6. Known DihydroPyrimidine Dehydrogenase (DPD) deficiency
7. Known allergy to Chinese hamster ovary cell proteins or other recombinant human or humanised antibodies or to any excipients of bevacizumab formulation, platinum compounds or to any other components of the study drugs

**Date of first enrolment**

01/01/2007

**Date of final enrolment**

31/10/2012

**Locations****Countries of recruitment**

United Kingdom

England

**Study participating centre**

Royal Marsden Hospital

Surrey

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## Sponsor information

### Organisation

Medical Research Council (UK)

### ROR

<https://ror.org/03x94j517>

## Funder(s)

### Funder type

Charity

### Funder Name

Cancer Research UK Clinical Trials Awards Advisory Committee (UK) (Grant No: C1504/A6410)

## 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? |
|---------------------------------------|---------|--------------|------------|----------------|-----------------|
| <a href="#">Results article</a>       | results | 01/03/2017   |            | Yes            | No              |
| <a href="#">Results article</a>       | results | 20/06/2019   | 21/06/2019 | Yes            | No              |
| <a href="#">Plain English results</a> |         |              |            | No             | Yes             |