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

Submission date
07/11/2006

Registration date
25/01/2007

Last Edited
24/09/2020

Recruitment status
No longer recruiting

Overall study status
Completed

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] 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
Prof David Cunningham

Contact details
Dept of Oncology
Royal Marsden Hospital
Downs Road
Sutton
Surrey
United Kingdom
SM2 5PT
+44 (0)20 8661 3156
David.Cunningham@rmh.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2006-000811-12

ClinicalTrials.gov (NCT)
NCT00450203

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

Study design
Open-label randomised controlled phase II/III clinical trial

Primary study design
Interventional

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^2 Intravenous [IV] day one
2. Cisplatin 60 mg/m^2 IV day one
3. Capecitabine 1250 mg/m^2 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 x 10^9/l
1.3. platelets more than 100 x 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 billirubin 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. Proteninuria 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 formulayion, 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

United Kingdom
SM2 5PT

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?
Results article	results	01/03/2017		Yes	No
Results article	results	20/06/2019	21/06/2019	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results				No	Yes