COUGAR-02

Randomised phase III study of docetaxel vs active symptom control in patients with relapsed oesophago-gastric adenocarcinoma

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STUDY OFFICE

For general queries, randomisation procedure, supply of trial materials and collection of data please contact the COUGAR-02 Trial Co-ordinator at The Cambridge Cancer Trials Centre,
Tel: 01223 216083; Fax: 01223 348071; E-mail: cctc@addenbrookes.nhs.uk

RANDOMISATION

To randomise a patient contact the Warwick-Clinical Trials Unit
Tel: 02476150402 (Mon-Fri, 9-5) Fax: 02476150549 (24hrs)

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Dr Hugo Ford

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1. INTRODUCTION

Carcinoma of the Oesophagus and stomach are respectively the 5th and 7th most common causes of death from cancer in the UK, between them accounting for more than 12,500 deaths per annum, more than any other individual cancer site apart from lung and colorectal cancer. Historically these cancers usually presented as distal gastric adenocarcinoma and proximal squamous cell carcinoma of the oesophagus, but the epidemiology of the disease has changed dramatically over the last 30 years, and in the UK today up to 70% of all oesophago-gastric cancers are adenocarcinomas of the distal oesophagus, oesophago-gastric junction or gastric cardia. Gastric cancer remains a major international health problem, and worldwide is the second most common cause of death from cancer. The treatment of advanced oesophago-gastric cancer (AOGC) is unsatisfactory. Although response rates of up to 55% are seen with modern chemotherapy regimens, the median survival is only approximately 9 months. A number of drugs demonstrate activity in oesophago-gastric cancer, but first-line therapy in Europe and the USA normally consists of combination therapy based on fluoropyrimidines and cisplatin or oxiplatin. Following failure of first-line chemotherapy outcomes are poor, and although a number of cytotoxic drugs such as irinotecan, oxaliplatin, paclitaxel and docetaxel have demonstrated activity (see below) no study has yet been performed which demonstrates that chemotherapy in this clinical situation is superior to best active symptom control. Notwithstanding this a high proportion of patients with AOGC in Europe and the US go on to receive second line therapy. Cytotoxic chemotherapy with these agents is expensive and potentially toxic. With poor response rates and outcomes overall many UK oncologists do not therefore routinely offer second-line therapy even to patients of good performance status, and practice in the UK and internationally is fragmented in this increasingly common clinical situation. With the publication of the MRC-OE02 and MRC-ST02 trial (MAGIC) trials an increasing number of patients with operable oesophago-gastric cancer will receive pre- or perioperative chemotherapy with a platinum/fluoropyrimidine combination. Even with this treatment, 65-70% of patients will have recurred within 5 years, and there is no standard therapy which can currently be offered on relapse[1]. There is therefore a need to demonstrate the superiority of systemic chemotherapy over active symptom control since there is no randomised trial data supporting either chemotherapy or

active symptom control. A number of agents have shown activity in this setting in small phase II studies, as detailed below.

Docetaxel: Two studies have assessed 3-weekly docetaxel as treatment for advanced gastric cancer. In the first, Vanhoefer et al[2] treated 27 patients with pretreated advanced gastric cancer (AGC) with docetaxel 100mg/m^2 every 3 weeks. The response rate was 27%, and survival data were not quoted. Subsequently Giuliani et al[3] assessed the same regimen in 30 patients with a response rate of 17% and median overall survival of 17% (1 yr survival 21%). Graziano et al[4] evaluated a weekly docetaxel schedule, however this appeared less effective, with only one response seen out of 21 patients treated. Metges et al[5] reported a phase II study of docetaxel in a mixed population of squamous and adeno-carcinomas of the oesophagus and reported a response rate of 28%. Conversely Heath et al[6] reported a response rate of 18% in chemonaive patients with oesophageal adenocarcinoma treated with docetaxel 75mg/m^2, but no responses in a small group of patients who had received prior chemotherapy.

Paclitaxel has also been assessed in phase II trials in relapsed AGC. Yoshida et al[7] treated 21 patients with paclitaxel 90mg/m^2 weekly, with a response rate of 19% and median survival of 8.6 months. Arai et al[8] treated 35 patients with paclitaxel 80mg/m^2/week with a response rate of 23% and median survival of 6.9 months. Cho et al[9] evaluated a similar regimen in 41 patients with a response rate of 40%. Furthermore Chang et al[10] have also tested the combination of paclitaxel 200mg/m^2 and carboplatin AUC 6 3-weekly in 42 patients with a response rate of 22% and median survival of 7.4 months.

Irinotecan-based therapy has been evaluated by Assersohn et al[11], who treated 40 patients with a combination of irinotecan 180mg/m^2 2-weekly with 5-FU and folinic acid. This trial showed the regimen to be well tolerated with a response rate of 29% and median survival 6.4 months. As a follow-up to this trial, the same group[12] also evaluated a 3-weekly combination of irinotecan 250mg/m^2 and capecitabine 2000mg/m^2 days 1-14 in 29 patients with advanced oesophago-gastric cancer. Response rate in this trial was 14% with median survival of 6.3 months. Another trial was carried out by Kim et al[13] in 64 patients previously treated with taxane plus

cisplatin. These patients received irinotecan 150mg/m^2 every 2 weeks with 5-FU and folinic acid. Response rate was 21% and median survival 7.6 months Weekly irinotecan 125mg/m^2 was used by Chun et al[14] in 37 patients with a response rate of 20% .Another group[15] has treated relapsed patients with a combination of oxaliplatin and 5-FU/folinic acid, with a response rate of 26% and overall survival of 7.3 months. Evidence from a randomised phase III trial of irinotecan versus best supportive care as 2nd line chemotherapy in gastric cancer (Thuss-Patience et al[16]) was stopped early due to poor accrual with 40 patients randomised over 4 years. With limited data, this trial showed a strong trend for improved survival with chemotherapy (median survival 123 days) compared to best supportive care (median 73 days, Hazard ratio = 0.48, 95% confidence interval 0.25-0.92, p = 0.023).

2. RATIONALE FOR THIS STUDY

From the above it can be seen that all the agents discussed are effective in a proportion of patients, but no single treatment stands out as superior. It is a widely held opinion in the oncology community that there are patients who benefit from chemotherapy, but no consensus as the appropriate regimen. Additionally the lack of evidence makes it difficult to justify the use of scarce resources. Treatment is therefore often guided by cost rather than evidence. The current study proposes to establish the role of chemotherapy for advanced oesophago-gastric cancer previously treated with a platinum/fluoropyrimidine combination or raltitrexed.

3. STUDY OBJECTIVES

3.1. Primary Objective

The primary objective is to compare overall survival in patients treated with docetaxel + active symptom control to those receiving active symptom control alone.

3.2. Secondary Objectives

For patients on the docetaxel arm (Arm A) of the study secondary objectives will be:

- Time to documented progression
- Response rates to docetaxel
- Toxicity of docetaxel

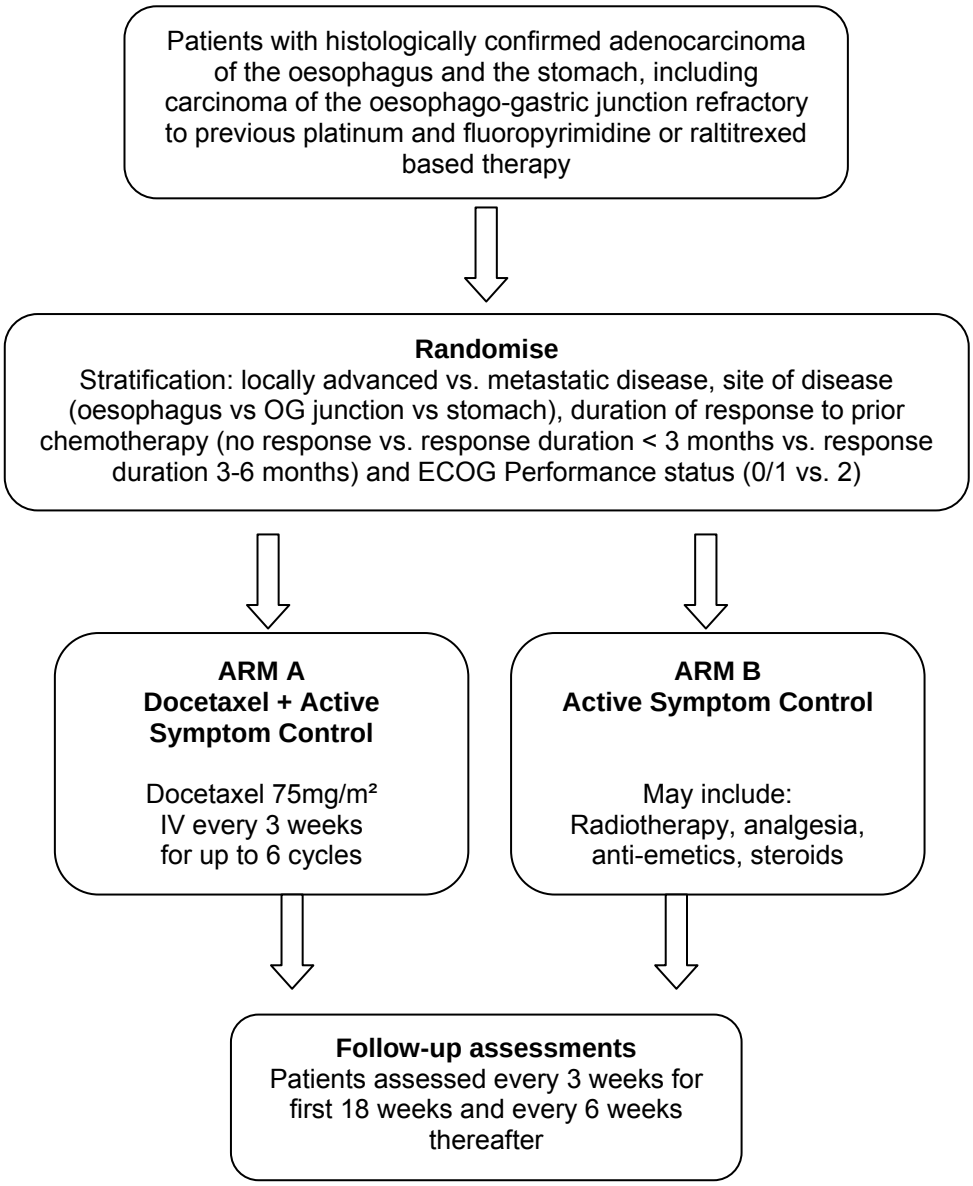
Patients on the two arms of the study will be compared for:

- Quality of life (QoL)
- Health Economic evaluation

4. STUDY DESIGN

4.1. Study Summary

A multicentre open-label, randomised controlled phase III trial of docetaxel vs active symptom control for patients with advanced oesophago-gastric adenocarcinoma who have relapsed within 6 months of previous chemotherapy.



4.2. Study Size

The study will recruit a minimum of 164 patients (82 patients in each arm) and a maximum of 180 patients (90 in each arm).

5. STUDY POPULATION

Patients must be determined to fulfill all entry criteria prior to randomisation.

5.1. Inclusion Criteria

- Age ≥18 years
- Histologically confirmed adenocarcinoma of the oesophagus or stomach (including adenocarcinoma of the oesophago-gastric junction)
- Advanced disease not amenable to curative treatment
- Documented progressive disease while receiving or within 6 months of completion of chemotherapy with a platinum and fluoropyrimidine or raltitrexed based therapy either for advanced disease or as neoadjuvant/perioperative therapy
- Estimated life expectancy of at least 12 weeks
- ECOG performance status 0,1 or 2 (Appendix 1)
- Satisfactory haematological (Hb ≥10g/dL, WBC ≥3.0 x 10^9/L, ANC ≥1.5 x 10^9/L, Plt ≥100 x 10^9/L), renal (Creatinine ≤Upper Limit of Normal (ULN), or measured/calculated Creatinine clearance ≥ 60 ml/min) and hepatic (T. Bili ≤ULN, ALT ≤ 1.5 x ULN, ALP ≤ 5 x ULN (for patients with liver metastasis) or ALP ≤ 2.5 x ULN (in absence of liver metastasis) function
- Written informed consent
- Completion of baseline QoL questionnaires (QLQ-C30, STO22 & EQ-5D)
- Female patients of childbearing potential must have had a negative pregnancy test 48 hours before entering the trial.
- Patients of both sexes with reproductive potential must employ barrier contraception whilst on treatment and for 3 months after completion of treatment.

5.2. Exclusion criteria

Patients with any of the following will not be eligible for entry into the study

- Cerebral or leptomeningeal metastasis
- Prior chemotherapy with taxanes
- Clinically significant peripheral neuropathy (Grade 2 to Grade 4) which in the view of the investigator would be a contraindication to taxane therapy

- Previous malignancy within the 5 years before study entry except for curatively treated basal cell carcinoma of the skin or cervical intraepithelial neoplasia
- Pregnant or breast-feeding women
- Any medical or psychiatric condition which would influence the ability of patients to provide informed consent
- Any other serious or uncontrolled illness which, in the opinion of the investigator, makes it undesirable for the patient to enter the trial

6. TREATMENT PLAN

6.1. Patients on Active Symptom Control (Arm B)

Active Symptom Control measures may include any or all of the following:

- Analgesics (including opioids)
- Anti-emetics
- Steroids
- Palliative radiotherapy
- Any other supportive measure deemed appropriate by the clinicians treating the patient.

All medications and procedures received by patients on this arm of the study must be reported in the Case Report Forms from the day of randomisation.

6.2. Patients on Docetaxel + Active Symptom Control (Arm A)

Patients must commence treatment with Docetaxel within 7 days of randomisation.

6.2.1. Administration of Docetaxel

The use of Docetaxel should be confined to units specialised in the administration of cytotoxic chemotherapy. Preparation and administration of Docetaxel should be in accordance to the current SmPC. From 21st June 2010, Sanofi-Aventis supplies Docetaxel as 1-vial concentrate for solution for infusion at 20mg/ml. This 1-vial presentation does not require prior dilution with a solvent and is ready to add to the infusion solution. Other Docetaxel medicinal products consisting of 2 vials

(concentrate and solvent) must not be mixed with this new Docetaxel presentation (1 vial only containing 20 mg/ml of docetaxel).

Docetaxel will be administered as an intravenous infusion over 1 hour at a dose of 75mg/m^2 in 250ml sodium chloride 0.9% solution or 5 % glucose solution every 3 weeks for a maximum of 6 cycles. Body surface area (BSA) will be calculated for each patient based on actual body weight at baseline. Patients will then receive the same dose at each treatment unless there is change in body weight of more than 10% from baseline, in which case the dose should be re-calculated.

6.2.2. Supply and Accountability of Docetaxel

A marketed formulation of Docetaxel will be supplied free of charge to all participating sites by the Sanofi-Aventis clinical operations team for use solely in the Cougar-02 clinical trial. The pharmacy department in each participating site will be responsible for ordering Docetaxel directly from Sanofi-Aventis using the Fax Order Form provided by the Cambridge Cancer Trials Centre (CCTC) during initiation of site.

Every participating site must inventory and acknowledge receipt of all shipments of Docetaxel and keep it in a locked area with restricted access. Storage and handling of the drug must be in accordance with the manufacturer's instructions as set out in the SmPC. The investigator or pharmacist at each site must keep accurate records of the Docetaxel quantities dispensed and used. At the conclusion of the study all unused study drug and medication containers will be destroyed as per local policy unless other arrangements have been approved by the Sponsor. All other appropriate drug forms (accountability, destruction, prescription) will also be provided by the (CCTC) if required.

6.2.3. Drug Labelling

The labelling of Docetaxel will be in accordance with all local legal requirements and conducted according to Good Manufacturing Practice. As a minimum, labels will include the following information:

- FOR CLINICAL TRIAL USE ONLY
- Study Title: Cougar-02 study

- EudraCT No: 2006-005046-37
- Sponsor: Cambridge University Hospitals NHS Foundation Trust
- Investigator: _____
- Site: _____
- Protocol Ref No.: _____
- Patient No.: _____
- Do not store above 25°C or below 2°C
- Expiry date:

6.2.4. Premedication

Patients should be premedicated with dexamethasone 8mg p.o. b.i.d. for 3 doses prior to each administration of Docetaxel i.e starting 1 day prior to Docetaxel administration (morning and evening) and about 1 hour before Docetaxel administration. It is recommended that steroids are also given following treatment, according to Docetaxel SmPC (i.e. 8mg p.o. b.i.d. for 3 doses), but local protocols are acceptable.

6.2.5. Active Symptom Control

Patients receiving docetaxel will also receive active symptom control as described in section 6.1.

All medications and procedures received by patients on either arm of the study must be reported in the Case Report Forms (CRFs) from the day of randomization.

6.2.6. Concomitant medication

In vitro studies have shown that the metabolism of Docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolized by cytochrome P450-3A such as ciclosporine, terfenadine, ketoconazole, erythromycin and troleandomycin. As a result caution should be exercised when giving these drugs as concomitant therapy to patients on Docetaxel since there is potential for significant drug-drug interaction.

6.2.7. Drug toxicities and dose modifications

Patients on the Docetaxel arm of the study will be reviewed for drug induced toxicities every three weeks prior to the start of next cycle of chemotherapy. Severity of each toxicity will be assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.
NCI CTCAE V3.0 can be found at and downloaded from the following website address: http://ctep.cancer.gov/reporting/ctc.html.

Table 1 summarises the most common, serious toxicities that may develop in patients treated with docetaxel and the recommended dose adjustments.

Table 1: Dose reductions for Docetaxel toxicities.

Toxicity	Severity	Management
Hypersensitivity	Grade 3/Grade 4	Administration of appropriate medication (see below)
Neutropenia	Day 1 neutrophil count <1.5x10^9/L	Stop treatment until ANC recovers to at least 1.5x10^9/L. Restart docetaxel at full dose (75mg/m^2)
	Febrile neutropenia **OR** Prolonged Grade 4 neutropenia (Neutrophil count < 0.5x10^9/L for 7 days or more)	Stop treatment until ANC ≥ 1.5x10^9/L. Restart drug at 55mg/m^2
Neuropathy	Grade 3 / Grade 4	Stop Docetaxel treatment
Thrombocytopenia	Platelet count < 100 x 10^9/L	Stop treatment until Plts ≥ 100x^9/L. Restart drug at full dose (75mg/m^2)
	Platelet count < 50 x 10^9/L (Grade 3/Grade 4)	Stop treatment until Plts ≥ 100x^9/L. Restart drug at 55mg/m^2
Hepatic dysfunction	T. Bili> ULN ALT/AST>1.5xULN ALP> 2.5xULN (in absence of liver metastasis) ALP > 5 x ULN (in presence of liver metastasis)	Stop Docetaxel until parameters recover to baseline levels. Restart drug at 55mg/m^2
Cutaneous reaction	Grade 2	Stop treatment until recovery to Grade 1 or better. Restart drug at full dose (75mg/m^2)
	Severe or cumulative (Grade 3/ Grade 4)	Stop treatment until recovery (Grade 1 or better). Restart drug at 55 mg/m^2

Other non-haematological toxicity	Grade 3/ Grade 4	Stop Docetaxel until parameters recover to baseline levels. Restart drug at 55mg/m^2

Hypersensitivity Reactions*:* Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. In order to reduce the incidence of hypersensitivity all patients should be premedicated with oral steroids (dexamethasone 8mg p.o. b.i.d. x 3 doses) - see section 6.2.4. If a significant reaction (Grade 3/Grade 4) occurs despite this, local protocols for the management of hypersensitivity reactions should be followed but would normally include the administration of chlorpheniramine 10-20 mg i.v. and hydrocortisone 100-500 mg i.v. In extreme cases adrenaline (1:1000 solution 0.5 mL i.m, repeated if necessary) may be required.

Neutropenia: This is the most frequent adverse reaction of docetaxel. For a new cycle of docetaxel treatment to be given the neutrophil count must be at least 1.5x10^9/L. Patients who develop neutropenia during treatment should stop taking docetaxel until their ANC has recovered to at least 1.5x10^9/L then restart drug at full dose (75mg/m2). Patients who develop febrile neutropenia or persistent neutropenia (Grade 4 neutropenia lasting for 7 days or more) should stop taking docetaxel until their ANC has recovered to at least 1.5x10^9/L Docetaxel should then be restarted at a reduced dose of 55mg/m^2 for subsequent cycles.

Thrombocytopenia: Patients who develop thrombocytopenia (Plt <100 x 10^9/L) should stop treatment until their platelets count recovers to ≥ 100x10^9/L. They can then restart treatment at full dose (75mg/m^2). If they suffer Grade 3 or Grade 4 thrombocytopenia (Plt < 50 x 10^9/L), treatment should be delayed until their platelet count recovers to ≥ 100x10^9/L and docetaxel may then be restarted at a reduced dose of 55mg/m^2 for subsequent cycles.

Neuropathy: Mild sensory neuropathy (Grade 1-2) may develop and persist for 3-4 months following completion of treatment. Patients who develop Grade 3 or 4 peripheral neuropathy should discontinue Docetaxel.

Hepatic dysfunction: If T.Bilirubin >ULN, ALT/AST > 1.5 x ULN and ALP > 2.5 x ULN (in absence of liver metastasis) or ALP > 5 x ULN (in presence of liver metastasis) treatment with docetaxel should be interrupted until these parameters recover to Grade 1 or baseline levels. Docetaxel can then be restarted at a reduced dose of 55mg/m^2.

Cutaneous reaction: If patients develop Grade 2 cutaneous reaction, docetaxel treatment should stop until this reaction resolves to G1 or better and then restart drug at full dose (75mg/m2). Patients who develop severe or cumulative (Grade 3-Grade 4) cutaneous reaction should stop treatment until resolution of skin changes. Treatment can then be restarted at a reduced dose of 55mg/m^2.

Any other Grade 3 or 4 non-haematological toxicity*:* Withhold docetaxel until parameters recover to baseline levels then restart at reduced dose of docetaxel at 55mg/m^2.

Patients who have already received one dose reduction and experience further toxicities which would require dose reduction (as defined above) should discontinue study medication.

Other, common, usually less serious toxicities expected from the use of docetaxel are described below:

Nausea and vomiting: This is usually mild but may occur in the first few days after chemotherapy. Treated with anti-emetics before each cycle of treatment at the discretion of the investigator.

Diarrhoea and Constipation: May occur in the first week of treatment and can be controlled by appropriate medication at the discretion of the investigator.

Alopecia (Hair loss): Usually starts to occur 3 weeks after the first injection of docetaxel and is temporary.

Muscle and joint pain: some patients may start experiencing these after 2-3 days of starting treatment.

Fluid retention: Weight gain and swelling in ankles and legs may occur during treatment but should decrease slowly following completion of treatment.

Effects on fertility and menstruation: Pre-menopausal female patients may notice disruption to their monthly periods and the drug may alter the function of the ovaries therefore affecting fertility. However, all female patients of child bearing potential must take adequate contraception during the course of treatment and for 3 months following completion of treatment.

If treatment is interrupted for toxicity the patient must be evaluated until resolution to Grade 0/ Grade 1 or baseline, then the patient can be re-treated provided there is no other reason for stopping treatment (as outlined in section 6.2.7 below).

6.2.8. Criteria for stopping Docetaxel treatment

- Completion of therapy (6 cycles)
- Delay of treatment for more than 21 days for any reason
- Unacceptable toxicity (life-threatening and/or irreversible toxicity not manageable by symptomatic care)
- Progressive disease (documented clinical or radiological progression)
- Development of any condition or occurrence of any event, which, in the opinion of the investigator, justifies discontinuation of treatment.
- Patient request

It is essential that all study documentation is completed. **Where patients stop trial treatment earlier than planned they must continue to complete QoL forms**, and clinical information should continue to be gathered and entered on to Case Report Forms as appropriate. As a minimum, follow-up data on progression, quality of life and survival status should be returned regularly.

Patients also have the right to withdraw consent from the study. In this case, data will no longer be collected.

7. STUDY PROCEDURES

7.1. Randomisation of patients

Randomisation will be stratified by the following factors: Locally advanced versus metastatic disease, site of disease (oesophagus versus oesophago-gastric junction versus stomach), duration of response to prior chemotherapy (no response versus response duration <3 months versus response duration 3-6 months), and ECOG performance status (0/1 versus 2).

Randomisation will be undertaken centrally by Warwick Clinical Trials Unit (WCTU) Local investigators in participating centres must obtain written informed consent from patients to participate in the study (see section 13.2) and check their eligibility for inclusion. After completing the Cougar-02 randomisation form investigators should contact the WCTU by telephone or fax (see below) where all eligibility criteria will be confirmed. The patient will then be randomly assigned to either Arm A or Arm B. A sequential trial number will be allocated, which must be recorded in the patient's records. The Investigator should inform the patients' GP of their participation in the study, subject to the patients' consent.

WARWICK CLINICAL TRIALS UNIT (WCTU)
RANDOMISATION LINE
Telephone 0247 6150402
Fax 0247 6150549

7.2. Study treatment period

Patients in the docetaxel arm (Arm A) must commence treatment within 7 days of randomisation. They will receive up to 6 cycles of Docetaxel at 3 weekly intervals. These patients will also receive active symptom control as required. Patients in Arm B will receive active symptom control as required from the date of randomisation. Patients in both arms of the study will be reviewed every 3 weeks for 18 weeks or until 3 weeks after receiving the last dose of chemotherapy, whichever is the later.

7.3. Follow-up Period

Following completion of Docetaxel treatment (Arm A) or after 18 weeks of active symptom control (Arm B) all patients must be followed up every 6 weeks in outpatients until the end of the first year or until death. Patients surviving beyond the first year of treatment will be followed up every 3 months until death.

8. PATIENT EVALUATION, ASSESSMENTS AND INVESTIGATIONS

8.1. Pre-Randomisation / Baseline Assessments

The following assessments must have been performed not more than 7 days prior to randomisation, unless otherwise indicated, and details recorded on the case report forms:

- History and physical examination
- EORTC QLQ-C30 and STO22 questionnaires (completed within 14 days prior to randomisation)
- Completion of concomitant medication record
- ECOG performance status
- Full Blood Count (Hb, WBC, ANC, Plts)
- Biochemistry (Creatinine, Urea, electrolytes, AST/ALT, ALP, T. Bili, calcium, glucose)
- CT scan of thorax and abdomen (within 28 days prior to randomisation).
- Documentation of progressive disease by radiological or clinical criteria. (Patients without measurable disease but evaluable disease are eligible for entry into the trial).
- EQ-5D questionnaire

8.2. Assessments During Study

Patients in Arm A will be reviewed before the administration of each cycle of docetaxel (every three weeks of treatment for up to 18 weeks unless there is a cycle delay). Patients in Arm B will be reviewed every three weeks for up to 18 weeks from randomisation. The following assessments will be made at each study visit:

- Clinical examination including performance status and weight
- Full Blood Count (Hb, WBC, ANC, Plts)
- Biochemistry (Creatinine, Urea, electrolytes, AST/ALT, ALP, T. Bili , calcium, glucose)
- Recording of all Adverse Events (both drug related and drug-unrelated)
- Recording of all concomitant medication and changes to medication
- Recording of any other concomitant anti-cancer treatment (e.g.

radiotherapy)

- CT scan of thorax and abdomen (only for patients on the Docetaxel arm of the study) after 3 and 6 cycles of treatment. Response to treatment will be assessed using RECIST criteria (version 1.0, 2000)
- EORTC QLQ-C30 and STO22 questionnaires (3,6,9,12 &18 weeks)
- EQ-5D and health resource use questionnaires

8.3. Assessments during Follow Up

The following assessments will be made during follow up visits (see section 7.3)

- Clinical examination including performance status and weight
- Recording of all concomitant medication and changes to medication
- Recording of any other concomitant anti-cancer treatment (e.g. radiotherapy)
- EORTC QLQ-C30 and STO22 questionnaires (only once, 24 weeks after randomisation)
- EQ-5D and health resource use questionnaires
- Other tests as clinically indicated

Table 2: Summary of all study related assessments and their timelines.

Assessment	Baseline	Every 3 weeks until 18 weeks	On completion of 3 and 6 cycles of docetaxel (Arm A only)	Follow up
Patient history	X			
Physical examination	X	X	X	X
ECOG Performance Status	X	X	X	X
FBC and Biochemistry	X	X	X	
Pregnancy test (if applicable)	X			
CT scan of thorax and abdomen	X		X*	
Disease assessment (RECIST)	X		X*	
Concomitant medication	X	X	X	X
Recording of any other cancer treatment	X	X	X	X
AE recording		X	X	
Completion of EORTC QLQ-C30 & STO22	X	X (3,6,9,12 & 18 weeks)	X	X**
Completion of EQ-5D	X	X	X	X
Completion of Patient resource use questionnaire		X	X	X
Completion of Health Economics Forms	X	X	X	X

* For patients on Arm A (Docetaxel + Active Symptom Control) only

**Only once, 24 weeks after randomisation

9. ADVERSE EVENTS

9.1. Definitions

An Adverse Event (AE) is any event, side effect or other untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0 will be used in this study. All toxic events will be graded according to NCI CTCAE V3.0.

NCI CTCAE V3.0 can be found at and downloaded from the following website address: http://ctep.cancer.gov/reporting/ctc.html.

A Serious Adverse Event (SAE) is any AE that meets any of the following criteria:

- **Results in Death,** regardless of cause, and occurring within 30 days of the last exposure to study therapy or after 30 days if it is a result of delayed toxicity.
- **Is Life-threatening** (immediate risk of death)
- **Requires hospitalisation or prolongation of existing hospitalisation, Results in persistent or significant disability / incapacity;**
- **Is a congenital abnormality / birth defect**
- **Is a new primary cancer diagnosis**

Please note that in the context of this trial the following do not need to be reported as SAEs:

- Disease progression or death as a result of disease progression
- Elective hospitalisation and surgery for further treatment of oesophago-gastric cancer
- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment.

- Elective hospitalisation for study therapy, disease related procedures or placement of an indwelling catheter, unless associated with other serious event.

These events should, however, be recorded on the patient CRFs.

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an AE that is both serious and unexpected, i.e. where the nature or severity of the event is not consistent with the information about the medicinal product in question set out either in the Summary of Product Characteristics (SmPC) or the Investigator Brochure (IB) for that product.

9.2. Assessment and reporting of Adverse Events

All adverse events will be assessed by the Investigator and recorded onto the appropriate pages of the patient CRF, including the date of onset, severity, duration, relationship to study therapy, and outcome.

All events should be graded according to the NCI CTCAE Toxicity Criteria (Version 3.0). For events not listed in the toxicity table, severity should be recorded as “mild”, “moderate”, “severe”, or “life-threatening”, according to the “other” category of the relevant section of the CTCAE Toxicity Criteria.

The Investigator will take all therapeutic measures necessary for resolution of any adverse event. Any medication necessary for treatment of the adverse event must be recorded onto the concomitant medications section of the patient’s CRF. If more than one adverse event occurs, each event should be recorded separately.

For patients on the Docetaxel + Active symptom control arm of the study (Arm A) AEs will be monitored and recorded from randomisation until 21 days after the last administration of study drug.
For patients on the Active symptom control arm of the study (Arm B) AEs will be monitored and recorded from the day of randomisation for 18 weeks.

The relationship of the AE to test medication will be assessed using the following definitions:

Not Related - There is not a temporal relationship to the study therapy, or there is a reasonable causal relationship between another drug, concurrent disease or circumstance and the event.

Unlikely to be related - There is little evidence to suggest there is a causal relationship to study therapy. There is another reasonable explanation for the event (e.g. the patient's clinical condition or concomitant treatments)

Possibly Related - The adverse event has a timely relationship to study therapy. However, a potential alternative aetiology exists, or dechallenge information is unclear.

Probably Related - The adverse event has a timely relationship to study therapy and a potential alternative aetiology is not apparent. The event responds to dechallenge.

Definitely Related - The adverse event has a timely relationship to study therapy and resolves when the drug is discontinued and a potential alternative aetiology is not apparent. Upon re-challenge with study therapy the event recurs.
'Unlikely' and 'Not Related' are considered not study drug related.
'Definitely', 'Probably' and 'Possibly' are considered study drug related.

9.3. Serious Adverse Event Reporting

For the Docetaxel+Active symptom control arm

All serious adverse events, regardless of relationship to investigational product, which occur from randomisation until 21 days after the final dose of study drug (Docetaxel) must be reported to the CCTC **within 24 hours of the investigator becoming aware of the event**. In addition, SAE's occurring after this time that are thought to be possibly related to treatment with the study drug, must also be promptly reported.

For the Active symptom control arm

All serious adverse events that occur from randomisation until 18 weeks thereafter must be reported to the CCTC within 24 hours of the investigator becoming aware of the event (but see section 9.1 above for those categories of events which do not require expedited reporting)

In the case of a **Serious Adverse Event** the Investigator must **immediately**:

FILL OUT a '**Serious Adverse Event Form'**

The form should be completed and signed by a member of the site trial team and faxed (within 24 hrs of becoming aware of the event) to the CCTC.

Fax number: 01223 348071

Even if only limited information is initially available, this should be provided and faxed on an SAE form. Further details should be submitted as soon as they become available.

In the case of **death, life-threatening events or SUSARs the investigator must:**

TELEPHONE (on day of awareness) the CCTC,

TEL: 01223 216083.

then FAX A COMPLETED SAE FORM to the CCTC

FAX: 01223 234071.

The CCTC will inform the relevant regulatory authorities (MHRA, Multicentre Research Ethics Committee (MREC)) within the specified timelines as well as Sanofi-Aventis within 24 hours by FAX. All reportable events (serious and unexpected and drug related/unknown relationship, and any others as advised by MREC), will be sent to Investigators.

Under the terms of the CTA for Docetaxel, any SUSAR reported to CCTC will also be reported to the Committee for the Safety of Medicines (CSM) by CCTC if thought "possibly", "likely" or "definitely" related to the study drug.

The CCTC will send a safety report to MREC annually and a copy to all investigational sites.

9.4. Follow-up of SAEs

In the case of a Serious Adverse Event, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

9.5. Pharmacovigilance

It is the responsibility of the local investigator to assess seriousness and causality when reporting SAEs to the sponsor. The study Sponsor will also independently determine the seriousness, causality and expectedness of the event. It is the responsibility of the sponsor or designee to report a serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR), as determined by the Chief Investigator, in the expedited time frame required according to UK requirements as well as any safety issues, to the relevant authorities: the Medicines and Healthcare products Regulatory Agency (MHRA) and the Multi-Centre Research Ethics Committee (MREC). It is also the responsibility of the sponsor to provide annual safety reports to these relevant regulatory authorities according to the EU Clinical Trial Directive and UK law.

10. EVALUATION OF OUTCOME

10.1. Primary Endpoint: Overall Survival

The primary endpoint of the trial is overall survival. Overall survival is measured as the time between the date of randomisation and the date of death from any cause. Surviving patients will be censored at the last known date alive.

10.2. Secondary Endpoint: Time to documented progression (Arm A only)

Time to documented progression is defined as the time between the date of randomisation and the date of tumour progression or the date of death from disease. Patients that are alive and progression-free are censored at the last known date alive and progression-free. Patients that died of non-disease related causes are censored at the date of death.

10.3. Secondary Endpoint: Response Rate (Arm A only)

Response will be assessed for patients receiving docetaxel chemotherapy only using the Response Criteria in Solid Tumours (RECIST)-(see Appendix 2) at baseline, and after 3 and 6 cycles of docetaxel (See Appendix 2). The best overall response achieved over the treatment period will be determined.

10.4. Secondary Endpoint: Toxicity (Arm A only)

For patients receiving Docetaxel treatment (Arm A) Adverse Events and Docetaxel related toxicity data will be collected at the end of each cycle of chemotherapy prior to the start of the next cycle and recorded in the patient CRFs. All Adverse Events related to Docetaxel treatment will be graded according to NCI CTCAE v3.0 (see section 9),

10.5. Secondary Endpoint: Quality of Life

Quality of life (QoL) is a secondary outcome measure. Patient-based outcomes using QoL measures are relevant to this study because second line chemotherapy is associated with side effects that may have a detrimental impact on QoL and these disadvantages need to be considered alongside possible survival advantages and

QoL benefits of chemotherapy that may occur with local tumour control. In addition for patients with recurrent oesophago-gastric cancer where overall survival is poor, robust assessment of QoL will inform future studies because there is a lack of high quality data in this area. Indeed, none of the phase II studies evaluating second line chemotherapy have reported QoL scores and a recently published systematic review of chemotherapy in advanced gastric cancer has concluded that QoL has been insufficiently evaluated in this area [17]. There is a lack of robust QoL assessment in randomised trials in oesophago-gastric cancer. If the trial demonstrates a clear survival advantage in one arm, provision of detailed QoL information alongside survival data allow patients to receive fully informed consent.

The main objective of QoL assessment within this clinical trial, therefore, is to describe the impact of second-line chemotherapy on physical, social and emotional well-being and compare it with the control group receiving best active symptom control. During chemotherapy it is hypothesised that patients in the intervention arm will report more problems with physical and social function and fatigue than the non-intervention arm. Problems with eating and swallowing however may be reduced during chemotherapy. After completion of chemotherapy QoL will be dependant upon disease progression in both groups of patients.

10.5.1. Quality of life measures

Quality of life will be assessed with the EORTC Quality of Life Questionnaire (QLQ-C30) version 3[18]. This is a generic cancer instrument composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social and cognitive function), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QoL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). All scales and single items meet the required standards for reliability and validity. This questionnaire lacks some dimensions that are relevant to QoL in patients with gastric cancer and these will be assessed with a disease specific module. The EORTC Quality of life group has designed and validated a site-specific module for stomach cancer (EORTC QLQ-STO22) [19, 20]. This includes scales assessing swallowing, eating, reflux and anxiety as well as single items related to treatment toxicity such as dry mouth and hair loss. This instrument has been widely used and validated in an international setting.

Patients are eligible for the QoL assessment in this study if they fulfil the eligibility criteria and complete the baseline QoL questionnaires before randomisation. Patients will be informed in the patient informed consent form that they will have their QoL assessment regularly while involved in this trial. QoL will be a secondary outcome and evaluated in a longitudinal design for all patients entered in this study.

10.5.2. Timing of Quality of Life Data Collection

Patients will be asked to complete QoL questionnaires within 14 days prior to randomisation whilst in the hospital for a scheduled visit. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is approximately 10-15 minutes. The clinical forms will include a question whether the QoL forms have been filled in and if not, the reason why. Subsequent questionnaires will be completed 3, 6, 9, 12, 18 and 24 weeks after randomisation, during scheduled clinic/study visits. This will total 7 QoL assessments per patient. The time window for completion of subsequent QoL questionnaires will be +/- 7 days of the scheduled assessment.

10.5.3. Compliance with Quality of Life Assessment

Missing data may hamper assessment of QoL in clinical trials. This may be because centres do not collect the questionnaires at the appropriate time (unit non-response), or because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average with the QLQ-C30 instrument and should not be a problem. The former problem is particularly important if patients have advanced cancer and low performance scores. It may be minimized by ensuring that participating centres are properly informed and motivated about QoL assessment. After randomisation the subsequent QoL assessments will be co-ordinated by the recruiting centre. Should serious volumes of missing questionnaires occur then the QoL assessment will be reviewed because it may require specialist support for data collection to be performed with home visits [21, 22].

10.6. Secondary Endpoint: Health Economic evaluation

The objective of the health economic evaluation is to identify the incremental cost effectiveness ratio for docetaxel+active symptom control compared to active symptom control only.

10.6.1. Measurement of outcomes

Economic evaluations are designed to inform resource allocation decisions and will be produced using the primary outcome measure of overall survival and Quality adjusted life years (QALYs) [23] Data on overall survival will be collected as part of the CRF.

The estimation of QALYs requires the production of utility weights for each health state observed in the trial population, which will be obtained using the EQ-5D instrument [24]. The EQ-5D will be completed at baseline and at every outpatient visit until death. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the health related QoL differences between therapies[25].

10.6.2. Measurement of resource use

The primary cost effectiveness analyses will adopt the perspective of the NHS and social services. NHS resource use associated with each treatment modality will be collected either through the CRF (hospital admissions, investigations, drugs, referrals for other services) or through a patient completed resource use questionnaire (contact with primary, community and social care services). The patient questionnaire incorporates tick-box completion where ever possible. Patients will receive and return their patient resource use questionnaire at every outpatient clinic until death, i.e. every 3 weeks for 18 weeks and subsequently every 6 weeks.

10.6.3. Unit costs

Unit costs for health service resources will be obtained from national sources such as the PSSRU, the BNF and NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit

cost estimate in the analysis. It is likely that the analysis time frame will be less than 12 months and therefore, by convention, discounting is not utilised.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size Calculation

It is difficult to determine reliable baseline estimates of survival in this situation, as the literature is sparse. The initial studies of chemotherapy versus active symptom control in the first-line setting suggest a median survival of approximately 3 months. These data are old however, and it is possible that advances in active symptom control have led to improvements in overall survival equating to a median survival of around 4 months. The median survival in published phase II studies for treated patients was 7.3 months. Recognising that this estimate is likely to be lower in a randomised study, the power calculations for the study were originally based on the assumption that chemotherapy would increase median survival from 4 to 6 months (Hazard ratio (HR) = 0.67). To detect this benefit assuming a 2 year recruitment period with analysis 6 months after completed recruitment with a power of 90% and a two sided alpha of 5% would require a total of 320 patients when accounting for a 10% drop-out rate.

However, a similar German trial of irinotecan versus best supportive care has recently been reported (Thuss-Patience et al[16]). The trial closed early due to poor accrual with 40 of the target 120 patients randomised, but even with their limited data, demonstrated a HR for survival of 0.48 (95% confidence interval 0.25-0.92) in favour of chemotherapy (p=0.02). Recognising that this may be optimistic given the small numbers recruited, a minimum total of 164 patients (82 on each arm) in Cougar-02 would be able to detect a HR of at least 0.64 (e.g. from a median of 3.5 to 5.5 months), assuming a 3.5 year recruitment period and analysis 6 months after completed recruitment with a power of 80% and a two-sided significance lever of 5%. Increasing the sample size to 180 patients (90 on each arm) would allow for dropouts, result in higher power or be able to detect a HR of 0.65 (e.g. from a median of 3.5 to 5.4 months). Hence the study aims to recruit a minimum of 164 patients and a maximum of 180 patients. The calculations are robust enough to account for various scenarios (see table 3).

Table 3: Calculations of the total sample size required to cover a range of potential survival benefits and power[26]

Median survival (months)		Power		
From	To	80%	85%	90%
2	3.5	102	118	138
2	4	68	76	90
2.5	4	146	168	196
2.5	4.5	94	54	126
3	5	126	144	170
3.5	5.4	178	204	238
3.5	5.5	164	188	220
3.5	5.8	132	150	176
3.5	5.9	124	142	166
3.5	6	116	132	156
4	6	206	236	276
4	6.3	166	188	238
4	6.7	128	148	172

Figures given are for the total sample size required in the study

11.2. Statistical Analyses

All analyses will be conducted on an intention-to treat basis, i.e. all patients randomised will be included, and all patients will remain in their randomised treatment groups, whatever treatment they receive.

Overall survival and time to documented progression will be analysed using Kaplan-Meier survival curves. The median survival times with appropriate confidence intervals will be reported. Differences in overall survival between randomised treatment arms will be compared using the log-rank χ^2 test and a Cox proportional hazards model will be used to adjust the treatment effect for stratification variables. The best response recorded for the patients having chemotherapy will be reported descriptively. Toxicity will be recorded descriptively in terms of incidence and worst severity.

QoL data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual[27]. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales. A high score for a symptom scale or item represents a high level of symptoms or problems. A high score for a functional scale represents a high or healthy level of functioning and a high score for the global health status/QL represents high QoL. Global and symptom-specific QoL scores will be compared between the two randomised groups.

An initial deterministic analysis will calculate the mean QALYs and the mean total direct cost of care for each randomisation arm. An incremental cost effectiveness ratio will then be calculated as the difference in between the mean costs and the difference in mean QALYs. The non-parametric bootstrap method will be used to produce a within-trial probabilistic sensitivity analysis of the incremental cost effectiveness ratio. The expected incremental cost effectiveness ratio, a scatterplot on the cost effectiveness plane, the 95% cost effectiveness ellipse and the cost effectiveness acceptability curve will be presented[23].

11.3. Study Duration and Milestones

COUGAR-02 will randomise a minimum of 164 patients and a maximum of 180 patients, from an estimated 33 UK centres treating oesophago-gastric cancer. The aim is to recruit these patients within a target accrual period of 3.5 years.

Patients in Arm A will receive up to 6 cycles of Docetaxel (one cycle every 3 weeks). Patients in both arms of the study will be reviewed every 3 weeks for 18 weeks or until the end of the Docetaxel treatment (whichever is later) then will be followed up until death, initially every 6 weeks until the end of the first year then every 3 months.

An analysis of the study data will be performed when there is a minimum of 6 months follow-up on all patients.

Recruitment of patients to the trial started in April 2008 and it is anticipated to be completed by February 2012.

Date	Anticipated Milestones
April 2008	Recruitment started
June 2010	First independent Data Monitoring Committee (DMEC).
June 2011	Second planned independent DMEC
January 2012	Third independent DMEC before official recruitment closure
February 2012	Anticipated completion of recruitment
August 2012	Anticipated planned analysis of primary outcome data

12. STUDY ORGANISATION

12.1. Trial responsibilities

The Trial Management Group is responsible for protocol development and initiation of the study. This group will form the basis for the Trial Steering Committee who will be responsible for monitoring study progress, amending the study protocol as required and overseeing the trial conduct and providing information to the independent Data Monitoring and Ethics committee (DMEC). Cambridge University Hospitals NHS Foundation Trust is the study sponsor and has responsibility for the initiation and management of the trial.

The Cambridge Cancer Trials Centre (CCTC) is responsible for the day-to-day running of the study, centre initiation and reporting to the Trial Steering Committee. The Warwick Clinical Trials Unit (WCTU) is responsible for randomisation, developing and maintaining the trial specific data base, the statistical analysis, reporting to the DMEC and presentation of results. Intellectual property and access to data arising from this trial will be governed by the Trial Steering Committee.

12.2. Site Responsibilities

The Principal Investigator at each participating centre has overall responsibility for the study and for all patients entered into the study, but may delegate responsibility down to other members of the study team as appropriate. The Principal Investigator must ensure that all staff involved in the study are adequately trained, and that their duties with regards to the trial have been entered on the Site Responsibilities and Signature Log. The Principal Investigator has responsibility for applying for site-specific

assessment for his/her individual site. Principal Investigators will be informed of the extension of favourable ethical opinion for their centre by a member of the Chief Investigator's team.

12.3. Study Start-up and Core Documents

Centres wishing to participate in the study should contact the CCTC to obtain information. The Principal Investigator will then be required to provide the CCTC with the following core documents and obtain all necessary approvals

- The site contact details (to include PI, research nurse, trial administration, pharmacist).
- Participating Site Agreement with the sponsor (signed by both sponsor and participating centre).
- A completed responsibility and signature log listing all staff participating in the trial. This form should be signed by the PI.
- Up to date CVs of all staff involved in the trial personally signed and dated. The CV should give details of education, training and experience relevant to the trial.
- Local R&D approval for the study.
- Laboratory normal ranges and accreditation certificates for the participating site.
- Copies of the Patient Information Sheet, GP letter and Consent form on local headed paper.

Following receipt of all the above documents the CCTC will arrange an initiation for each participating centre before the site becomes activated.

12.4. Data Collection

All trial related data collected for each patient needs to be reported on Case Report Forms (CRFs). These will be provided to each participating centre by the CCTC. Data collected on each patient will be recorded by the investigator, or designated member of staff, as accurately and completely as possible as soon as the requested information is available. The investigator will be responsible for the timing, completeness, legibility and accuracy of the Case Report Forms (CRFs). The

completed CRFs will be returned to the CCTC but copies will be kept by the Investigator. The investigator will supply the CCTC with any required background data from such records.

Entries will be made in black ballpoint pen on the CRF provided and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator, or designated member of staff. If it is not clear why a change has been made, an explanation should be written next to the change. Typing correction fluid should not be used. Each patient enrolled into the study must have a CRF completed and signed by the Principal Investigator. This also applies to those patients who fail to complete the study. Data reported on the CRF should be consistent with the source data, with any discrepancies explained.

To enable peer review and / or audits from Health Authorities, the Investigator must agree to keep all relevant records, including the identity of participating subjects (with sufficient information to link records, e.g. CRFs and hospital records), all original signed Informed Consent Forms, copies of all CRFs and detailed records of drug dispensing. To comply with international regulations, the records should be retained by the Investigator for 15 years, including assessments such as CT scans.

12.5. Data storage

Details of participating sites and staff will be recorded during the study by the CCTC and any changes to these will be recorded in timely fashion in order to maintain accurate details of personnel and status.

A study specific database will be created by Warwick Clinical Trials Unit and this will hold all details of patients randomized to the trial and all patient data collected on CRFs during the study. Data from CRFs will be modified to correct any erroneous or missing entries. The reasons for such changes will be recorded for audit purposes.

At the conclusion of the trial, when all patient data has been collected, and the analysis is complete, all the data stored on the computer system will be archived for 15 years. After trial conclusion, if any audit is required or new analyses are to be performed, the data may be retrieved, subject to approval from the TSC.

12.6. Monitoring

The CCTC has responsibility for the conduct of the study according to the current guidelines for Good Clinical Practice (GCP). Participating centres will be monitored by CCTC staff to confirm compliance with the protocol, the current guidelines for Good Clinical Practice, and the protection of patients' rights as detailed in the Declaration of Helsinki.

Participating centres will be monitored by checking incoming forms for compliance with the protocol, consistent data, missing data and timing. Study staff will be in regular contact with CCTC personnel (by phone/fax/e-mail/letter) to check on progress and deal with any queries they may have.

Periodic monitoring visits may be carried out where necessary. Centres may be suspended from further recruitment in the event of serious and persistent non-compliance and / or very poor recruitment.

13. ETHICAL AND REGULATORY CONSIDERATIONS AND INFORMED CONSENT

13.1. Ethical Approval

This study will be conducted in accordance with the principles of the declaration of Helsinki (1964) and as amended in Tokyo (1975), Venice (1983), Hong Kong (1989) South Africa (1996), Scotland (2000), Seoul (2008)

Multicentre Reseach Ethics Committee (MREC) approval has been obtained for this trial. The CCTC will maintain contact with MREC and will submit any protocol amendments to them. The CCTC will forward any resulting documentation to participating centres. It will be the responsibility of the local Principal Investigators to obtain the necessary local approvals (including Site Specific Approval, and local R&D approval) for the study as well and any necessary local approvals for subsequent amendments.

The CCTC will send an annual study progress report to the MREC and a copy to all participating centres.

13.2. Patient informed consent

The local investigator is required to explain the nature and purpose of the study to the patient prior to study entry. A patient information sheet will be given to the patient to take away and read in his/her own time. Written informed consent must be obtained before study entry and before any study related procedures can be carried out.

The patient information sheet and consent form will be available in electronic format from the CCTC to enable individual hospitals to put onto their headed paper.

13.3. Patient withdrawal.

Patients have the right to withdraw from the study at any time for any reason. The investigator has the right to stop study treatment for medical or safety reasons. These patients will normally stay in the study unless consent is withdrawn. Full details of the reasons for withdrawal should be recorded on the appropriate CRFs. Patients withdrawn from the study should, where possible, be followed up in accordance with the protocol.

13.4. Regulatory Status

The trial has a Clinical Trial Authorisation (CTA) from the MHRA. The CTA is conditional on all suspected unexpected serious adverse drug reactions (SUSARs) being reported promptly to the CCTC who will forward them to the committee on Safety of Medicines (CSM). The CCTC will be responsible for registering all new investigators.

13.5. Notification of amendments

Amendments are changes made to the research protocol after a favourable ethical opinion has been given. Substantial amendments include any changes that: affect the safety or physical/mental integrity of trial subjects; the scientific value of the trial; the conduct or management of the trial; the quality or safety of the IMP. The sponsor is

responsible for notifying all substantial amendments to the main MREC that gave a favourable opinion and to the MHRA. All protocol amendments agreed by the trial steering committee will be submitted to the MREC and the MHRA prior to submission to any local authorizing bodies.

14. PROTOCOL COMPLIANCE

Staff at the CCTC will be in regular contact with personnel in all participating centres to check on progress and to assist with any queries that may arise. Incoming case report forms will be checked for completeness, consistency, timeliness and compliance with the protocol. Centres may be withdrawn from the trial in the event of serious and persistent non-compliance.

15. INDEMNITY

Cambridge University Hospitals NHS Foundation Trust, as a member of the NHS Clinical Negligence Scheme for Trusts, will accept full financial liability for harm caused to participants in the clinical trial caused through the negligence of its employees and honorary contract holders. There are no specific arrangements for compensation should a participant be harmed through participation in the trial, where no-one has acted negligently.

16. DATA PROTECTION AND PATIENT CONFIDENTIALITY

The CCTC and Warwick Clinical Trials Unit will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Patients should be reassured that their confidentiality will be respected at all times.
Data will be stored in a secure manner and in compliance with the data protection act 1998. The study will be registered with the data protection officer at Addenbrooke's Hospital.

The personal data recorded on all documents will be regarded as strictly confidential. To preserve the patient's anonymity, only their initials, date of birth and hospital number will be recorded on all CRFs. The investigator must ensure the patient's anonymity is maintained. The investigator must maintain documents not for submission to the trial unit (e.g. written consent forms) in strict confidence.

17. INDEPENDENT DATA MONITORING AND ETHICS COMMITTEE (DMEC) AND INDEPENDENT TRIAL STEERING COMMITTEE (TSC)

Interim study data containing recruitment, safety and outcome data will be reviewed by an independent DMEC consisting of at least 2 clinicians not entering patients into the trial and an independent statistician. The DMEC will recommend whether the accumulated data from the trial, together with the results from other relevant trials justifies continued recruitment of further patients. A decision to discontinue recruitment will be made only if the result is likely to be accepted by a range of clinicians including study participants. Although no formal stopping guidelines are specified, the DMEC may consider using a p value <0.001 to be an indicator of the strength of evidence that needs to be reached. If a decision is made to continue the DMEC will advise on the frequency of future reviews of the data on the basis of accrual and event rates, although annual meetings are anticipated. The DMEC will make confidential recommendations to the TSC.

The role of the TSC is to act on behalf of the sponsor and funders to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP and to provide advice through its independent chairman. This independent committee will review the recommendations from the DMEC and will decide on continuing or stopping the trial, or modifying the protocol. The membership of the committee will include an independent chairman and not less than two other independent members in addition to the chief investigator, chief statistician and one other principal investigator. The TSC will meet at least annually, and observers from the MRC and the sponsor will be invited to meetings.

The Trial Management Group (TMG) is responsible for the day-to-day co-ordination of the trial and related activities. The composition of the TMG is stated on page 2 of the study protocol.

18. PUBLICATION POLICY/DATA SHARING

Data from all centres will be collected and published as soon as possible. Individual centres may not publish data on their patients that are directly relevant to the questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the writing committee.

All publications will include a list of participants, and the named authors will include the chief investigator, clinical trial co-ordinator and statistician involved in the trial.

All requests for data accrued in the trial shall be submitted to the chief investigator. These requests will be considered by the TMG and if approved will be released subject to the agreement of the Trial Steering Committee (TSC).

19. FUNDING

The study is funded by Cancer Research UK (grant number C21276/A7737; study ref: CRUK/07/013) and supported by the National Cancer Research Institute Upper Gastrointestinal Clinical Studies Group which includes patient representation. The study drug, Docetaxel is provided free of charge from Sanofi Aventis.

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APPENDIX 1

ECOG PERFORMANCE STATUS SCALES

Point	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

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APPENDIX 2

RESPONSE CRITERIA IN SOLID TUMOURS (RECIST) version 1.0 QUICK REFERENCE GUIDE

Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.

  Measurable disease - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

  Measurable lesions - lesions that can be accurately measured in at least one dimension with longest diameter ≥20 mm using conventional techniques or ≥10 mm with spiral CT scan.

  Non-measurable lesions - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.

- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline documentation of "Target" and "Non-Target" lesions

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured at baseline.

- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

- All other lesions (or sites of disease) should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Response Criteria

Evaluation of target lesions

*Complete Response (CR):	Disappearance of all target lesions
*Partial Response (PR):	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
*Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
*Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

Although a clear progression of "non target" lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol.

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