

## Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02)

Ford, Hugo E R; Marshall, Andrea; Bridgewater, John A; Janowitz, Tobias; Coxon, Fareeda Y; Wadsley, Jonathan; Mansoor, Wasat; Fyfe, David; Madhusudan, Srinivasan; Middleton, Gary; Swinson, Daniel; Falk, Stephen; Chau, Ian; Cunningham, David; Kareclas, Paula; Cook, Natalie; Blazeby, Jane M; Dunn, Janet A; COUGAR-02 Investigators

DOI:

[10.1016/S1470-2045\(13\)70549-7](https://doi.org/10.1016/S1470-2045(13)70549-7)

License:

Creative Commons: Attribution (CC BY)

*Document Version*

Publisher's PDF, also known as Version of record

*Citation for published version (Harvard):*

Ford, HER, Marshall, A, Bridgewater, JA, Janowitz, T, Coxon, FY, Wadsley, J, Mansoor, W, Fyfe, D, Madhusudan, S, Middleton, G, Swinson, D, Falk, S, Chau, I, Cunningham, D, Kareclas, P, Cook, N, Blazeby, JM, Dunn, JA & COUGAR-02 Investigators 2014, 'Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial', *The Lancet Oncology*, vol. 15, no. 1, pp. 78-86. [https://doi.org/10.1016/S1470-2045\(13\)70549-7](https://doi.org/10.1016/S1470-2045(13)70549-7)

[Link to publication on Research at Birmingham portal](#)

### **Publisher Rights Statement:**

Checked for eligibility: 16/01/2018

### **General rights**

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

### **Take down policy**

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact [UBIRA@lists.bham.ac.uk](mailto:UBIRA@lists.bham.ac.uk) providing details and we will remove access to the work immediately and investigate.



# Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial



Hugo E R Ford, Andrea Marshall, John A Bridgewater, Tobias Janowitz, Fareeda Y Coxon, Jonathan Wadsley, Wasat Mansoor, David Fyfe, Srinivasan Madhusudan, Gary W Middleton, Daniel Swinson, Stephen Falk, Ian Chau, David Cunningham, Paula Kareclas, Natalie Cook, Jane M Blazeby\*, Janet A Dunn\*, on behalf of the COUGAR-02 Investigators

*Lancet Oncol* 2014; 15: 78–86

Published Online

December 10, 2013

[http://dx.doi.org/10.1016/S1470-2045\(13\)70549-7](http://dx.doi.org/10.1016/S1470-2045(13)70549-7)

See [Comment](#) page 8

Copyright © Ford et al. Open Access article distributed under the terms of CC BY

\*These authors contributed equally

Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK (H E R Ford MD, T Janowitz PhD, P Kareclas PhD, N Cook PhD); Warwick Clinical Trials Unit, Coventry, UK (A Marshall PhD, Prof J A Dunn PhD); University College London Cancer Institute, Huntley Street, London, UK (J A Bridgewater PhD); Newcastle General Hospital, Newcastle, UK (FY Coxon MRCP); Weston Park Hospital, Sheffield, UK (J Wadsley FRCP); Christie Hospital, Manchester, UK (W Mansoor PhD); Lancaster Royal Infirmary, Lancaster, UK (D Fyfe MD); Queens Medical Centre, Nottingham, UK (S Madhusudan FRCP); Royal Surrey County Hospital, Guildford, UK (Prof G W Middleton MD); St James' University Hospital, Leeds, UK (D Swinson MD); Bristol Haematology and Oncology Centre, Bristol, UK (S Falk MD); Royal Marsden Hospital, Sutton, UK (I Chau MD, Prof D Cunningham MD); and University of Bristol, Bristol, UK (Prof J M Blazeby MD)

Correspondence to: Dr Hugo E R Ford, Box 193, Addenbrooke's Hospital, Hills Rd, Cambridge CB2 0QQ, UK. [hugo.ford@addenbrookes.nhs.uk](mailto:hugo.ford@addenbrookes.nhs.uk)

## Summary

**Background** Second-line chemotherapy for patients with oesophagogastric adenocarcinoma refractory to platinum and fluoropyrimidines has not shown benefits in health-related quality of life (HRQoL). We assessed whether the addition of docetaxel to active symptom control alone can improve survival and HRQoL for patients.

**Methods** For this open-labelled, multicentre trial, we recruited patients aged 18 years or older from 30 UK centres. Patients were eligible if they had an advanced, histologically confirmed adenocarcinoma of the oesophagus, oesophagogastric junction, or stomach that had progressed on or within 6 months of treatment with a platinum-fluoropyrimidine combination. Patients could have an Eastern Cooperative Oncology Group performance status of 0–2. We randomly assigned patients using a central, computerised minimisation procedure to receive docetaxel plus active symptom control, or active symptom control alone (1:1; stratified by disease status, disease site, duration of response to previous chemotherapy, and performance status). Docetaxel was given at a dose of 75 mg/m<sup>2</sup> by intravenous infusion every 3 weeks for up to six cycles. The primary endpoint was overall survival, analysed by intention to treat. This is the report of the planned final analysis. This study is an International Standardised Randomised Controlled Trial, number ISRCTN13366390.

**Findings** Between April 21, 2008, and April 26, 2012, we recruited 168 patients, allocating 84 to each treatment group. After a median follow-up of 12 months [IQR 10–21]) and 161 (96%) deaths (80 in the docetaxel group, 81 in the active symptom control group), median overall survival in the docetaxel group was 5.2 months (95% CI 4.1–5.9) versus 3.6 months (3.3–4.4) in the active symptom control group (hazard ratio 0.67, 95% CI 0.49–0.92;  $p=0.01$ ). Docetaxel was associated with higher incidence of grade 3–4 neutropenia (12 [15%] patients *vs* no patients), infection (15 [19%] patients *vs* two [3%] patients), and febrile neutropenia (six [7%] patients *vs* no patients). Patients receiving docetaxel reported less pain ( $p=0.0008$ ) and less nausea and vomiting ( $p=0.02$ ) and constipation ( $p=0.02$ ). Global HRQoL was similar between the groups ( $p=0.53$ ). Disease specific HRQoL measures also showed benefits for docetaxel in reducing dysphagia ( $p=0.02$ ) and abdominal pain ( $p=0.01$ ).

**Interpretation** Our findings suggest that docetaxel can be recommended as an appropriate second-line treatment for patients with oesophagogastric adenocarcinoma that is refractory to treatment with platinum and fluoropyrimidine.

**Funding** Cancer Research UK.

## Introduction

Globally, gastric cancer is the fourth most common type of cancer, with 989 000 new cases a year, and oesophageal cancer is the seventh, with 482 000 new cases a year.<sup>1</sup> Patients are most commonly diagnosed with locally advanced or metastatic oesophagogastric cancer, except for in Asia, where screening programmes for gastric cancer are common. For patients with advanced or metastatic disease, outcomes are poor: median overall survival is 8–12 months with first-line chemotherapy. Even after combination treatment including surgery, more than half of patients in western populations relapse.<sup>2</sup> When relapse or progression occurs after first-line treatment, median overall survival with supportive care is only 3–4 months.<sup>3</sup> The high global incidence of oesophagogastric cancer, the high relapse rate, and the

short survival after relapse or progression indicate an urgent need for effective second-line treatment.

When we planned this trial, we knew of no randomised data indicating any benefit to second-line chemotherapy. The best evidence consisted of small (fewer than 50 patients) phase 2 trials, findings from which had suggested tumour responses with different chemotherapy agents including irinotecan<sup>4</sup> and docetaxel.<sup>5</sup> The largest series reported 154 patients treated with docetaxel 75 mg/m<sup>2</sup> of body surface area every 3 weeks after failure of a platinum and fluoropyrimidine combination, with a response rate of 14% and median overall survival of 7.2 months.<sup>6</sup> However, potential for toxicity from chemotherapy is high in this group of patients with a poor prognosis, and there was no evidence that chemotherapy improved either survival or health-related quality of life (HRQoL).

We therefore aimed to assess the benefits of second-line docetaxel in patients whose disease had progressed within 6 months of previous chemotherapy. In particular, we aimed to find out whether any survival benefit came with an improvement in HRQoL.

## Methods

### Study design and patients

This multicentre, open-label, randomised, controlled phase 3 trial was designed by the COUGAR-02 Trial Management Group under the auspices of the Upper Gastrointestinal Cancer Clinical Studies Group of the UK National Cancer Research Institute. We did the study in 30 UK sites. Patients at least 18 years old with histologically confirmed adenocarcinoma of the oesophagus, oesophagogastric junction, or stomach were eligible for inclusion if they had advanced disease and documented disease progression during or within 6 months of treatment with platinum and fluoropyrimidine-based treatment (which could have been given as adjuvant or neoadjuvant therapy, or for advanced disease). Patients with disease-free intervals longer than 6 months were not eligible because the most common UK practice is that patients with a treatment-free interval of more than 6 months with chemotherapy would be either re-challenged with the original chemotherapy or offered second-line chemotherapy. We felt that it was not appropriate to offer these patients active symptom control. Further inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (normal) to 2 (symptomatic but in bed or chair less than 50% of waking hours);<sup>7</sup> satisfactory haematological, renal, and hepatic function; and completion of baseline HRQoL questionnaires—European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) and EORTC QLQ-STO22.<sup>8–10</sup> Eligible patients had baseline haemoglobin greater than 100 g/L for study entry. Important exclusion criteria were previous chemotherapy with a taxane, grade 2–4 peripheral neuropathy, previous malignancy, and cerebral or leptomeningeal metastases. All participants provided written informed consent. Central randomisation, data storage, and analysis were done by the Warwick Clinical Trials Unit (Coventry, UK). Trial coordination and pharmacovigilance was done by the Cambridge Cancer Trials Unit—Cancer Theme (Cambridge, UK). We obtained Multicentre Research Ethics Committee (MREC) approval from the UK National Research Ethics Service Committee South West-Exeter MREC (Bristol, UK). All aspects of the study were done in accordance with the Declaration of Helsinki including all of its relevant amendments, the guidelines for Good Clinical Practice of the International Conference on Harmonization, and all relevant UK and European laws and directives. An independent data monitoring and ethics committee monitored recruitment, safety, and outcome.

### Randomisation and masking

This was an open-label study. We randomly allocated patients in a 1:1 ratio to either docetaxel plus active symptom control (docetaxel group) or active symptom control alone using a central computerised minimisation procedure generated at the Warwick Clinical Trials Unit. Trial allocations were stratified by disease status (locally advanced *vs* metastatic disease), disease site (oesophagus *vs* oesophagogastric junction *vs* gastric), duration of response to previous chemotherapy (no response *vs* response duration <3 months *vs* response duration 3–6 months), and performance status (0–1 *vs* 2). To conceal the sequence the investigator or research nurse, who recruited the patients, contacted the Warwick Clinical Trials Unit for each participant's random allocation sequence. Because this was an open-label study, participants, investigators, and trials staff were aware of treatment allocations.

### Treatment

Active symptom control was offered to all patients participating in the trial, and was delivered according to local pathways within each participating hospital and included community and hospice care. Docetaxel was given at a dose of 75 mg/m<sup>2</sup> of body-surface area by intravenous infusion over 1 h every 3 weeks for up to six cycles, which was the standard dose and schedule in the UK at the time of the study. We gave patients dexamethasone 8 mg orally, two times a day for three doses before each administration of docetaxel—ie, dexamethasone treatment starting 1 day before docetaxel administration (morning and evening) and about 1 h before docetaxel administration. We stipulated in the protocol that steroids were also given after treatment (ie, 8 mg orally, two times a day for three doses), but local protocols were accepted. Hypersensitivity reactions were managed with supportive drugs as defined in the protocol. Dose modification for haematological toxicity was based on a blood test before each cycle of chemotherapy. If the absolute neutrophil count (ANC) was greater than  $1.5 \times 10^9$  cells per L or platelet count was above  $100 \times 10^9$  per L then treatment was continued at full dose. If a patients' ANC was below  $1.5 \times 10^9$  cells per L treatment was delayed until recovery. If ANC recovered to greater than  $1.5 \times 10^9$  cells per L within 14 days then treatment was restarted. Subsequent treatments were given at full dose unless there was lengthy grade 4 neutropenia (ANC less than  $0.5 \times 10^9$  cells per L for more than 7 days) or febrile neutropenia, in which case the dose of docetaxel was reduced to 55 mg/m<sup>2</sup> of body-surface area for subsequent cycles. If neutropenia persisted for more than 14 days no further docetaxel was given. If a patients' platelet count was below  $100 \times 10^9$  per L treatment was delayed until recovery. If the platelet count recovered to greater than  $100 \times 10^9$  per L within 14 days then treatment was restarted. Subsequent treatments were given at full dose unless the platelet count had fallen to less than  $50 \times 10^9$  per L, in which

case the dose of docetaxel was reduced to 55 mg/m<sup>2</sup> of body-surface area for subsequent cycles. If thrombocytopenia persisted for more than 14 days no further docetaxel was administered. In the event of hepatic toxicity, defined as bilirubin greater than upper limit of normal, alanine aminotransferase or aspartate aminotransferase greater than 1.5 times the upper limit of normal, alkaline phosphatase greater than 2.5 times the upper limit of normal in the absence of liver metastases, or alkaline phosphatase greater than 5 times the upper limit of normal in the presence of liver metastases, then treatment was delayed until recovery and the dose of docetaxel was reduced to 55 mg/m<sup>2</sup> of body-surface area for subsequent cycles. Non-haematological toxicity was managed as follows: for cutaneous toxicity of grade 2 or greater, docetaxel was stopped until recovery to baseline. For grade 2 toxicity subsequent treatments were given at full dose, whereas in the event of grade 3 or 4 toxicity, the dose of docetaxel was reduced to 55 mg/m<sup>2</sup> of body-surface area for subsequent cycles. Treatment was permanently discontinued if patients developed grade 3–4 peripheral neuropathy. For all other grade 3–4 non-haematological toxicities, treatment was interrupted until resolution and the dose of docetaxel was reduced to 55 mg/m<sup>2</sup> of body-surface area for subsequent cycles.

See Online for appendix

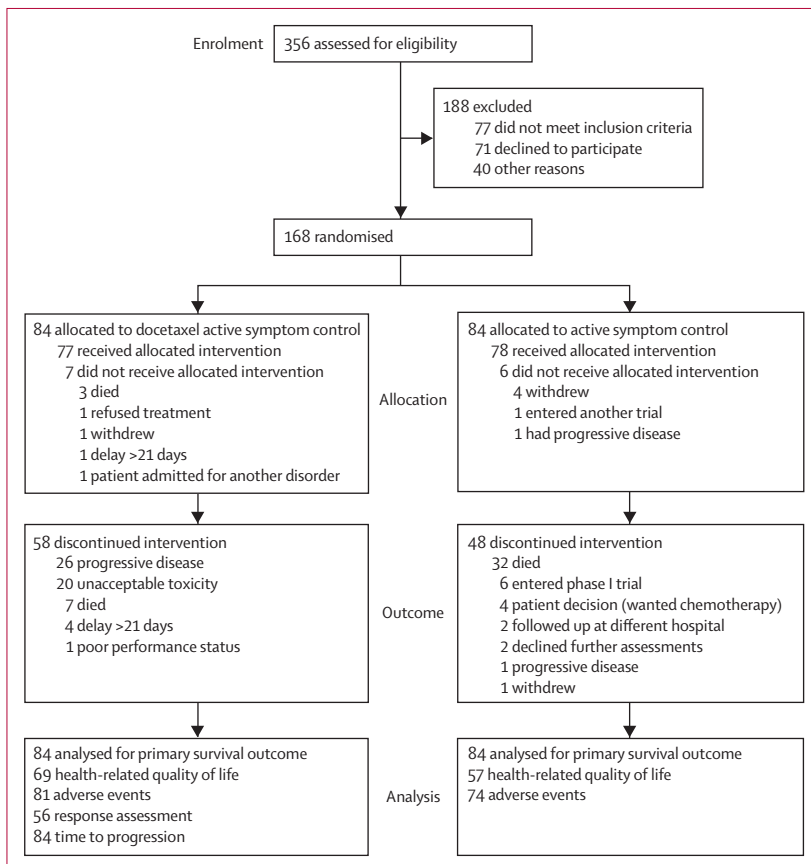


Figure 1: Trial profile

Docetaxel was discontinued on completion of six cycles, delay of treatment for more than 21 days, disease progression, unacceptable toxicity, or patient request.

We reviewed patients on active symptom control alone every 3 weeks for the 18-week treatment period. Patients receiving docetaxel were reviewed before each cycle. In both trial groups, we assessed toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0). At baseline and at each study visit a patient's status was assessed by medical history, physical examination including performance status and weight, full blood count, and biochemical serum analysis. HRQoL questionnaires were handed out at weeks 3, 6, 9, 12, 18, and 24 on arrival at clinic visits for patients to complete themselves. We did CT scans of patients' thorax and abdomen at baseline and after cycles three and six for patients receiving docetaxel. We measured and interpreted tumour according to RECIST (version 1.0) guidelines.<sup>11</sup>

On completion of docetaxel or after 18 weeks, patients were followed up every 6 weeks for up to 1 year. After 1 year, patients were reviewed every 3 months until death.

### Statistical analysis

The primary endpoint was overall survival. We needed a sample size of 320 patients to detect a median overall survival gain from 4 months to 6 months, assuming patients were recruited over a 2 year period and were followed up for a minimum of 6 months, with 90% power and two-sided alpha of 0.05. While the study was underway, a randomised trial was published that suggested a survival advantage for chemotherapy and a poorer overall survival for patients given active symptom control than we had assumed.<sup>12</sup> We recalculated the sample size on the recommendation of the first independent data monitoring and ethics committee in June, 2010, on the basis of poorer recruitment than expected and assuming a lower overall survival in the control group. A revised minimum total of 164 patients was therefore needed to detect a hazard ratio of 0.64, assuming 3.5 years recruitment, a two-sided alpha of 0.05, and 80% power, but was sufficient to accommodate a range of potential outcomes (appendix).<sup>13</sup>

Secondary endpoints were best response to docetaxel, time to documented disease progression (for the docetaxel group), toxicity, and HRQoL. Important HRQoL endpoints identified before we started the study were physical and social function and fatigue (QLQ-C30) and eating restrictions and dysphagia (QLQ-STO22).

We did all analyses on an intention-to-treat basis. We calculated overall survival from date of randomisation until date of death, censoring at the last known date alive. We calculated time to documented disease progression within 24 weeks from date of randomisation until date of progression, or death from disease without recorded progression if within 24 weeks. We constructed survival curves using the Kaplan-Meier method.<sup>14</sup> We

compared survival differences using a Cox proportional hazard model and calculated hazard ratios with 95% CIs.<sup>15</sup> We did a planned multivariate Cox-regression analysis for overall survival to adjust the treatment effect for the stratification variables. We calculated hazard ratios for prognostic subgroups and constructed a hazard ratio plot.<sup>16</sup>

The delivered dose intensity for docetaxel was calculated as the ratio of actual dose received per week to the expected dose averaged over the number of cycles administered.

We analysed HRQoL data with a standardised area under the curve analysis and compared them using Wilcoxon rank sum tests.<sup>17</sup> We handled missing questionnaire data by calculating the scale score if at least half of items were answered.<sup>18</sup> We did sensitivity analyses adjusting for dropouts due to death using a quality-adjusted survival analysis for the global HRQoL score.<sup>19</sup>

Reported p values are two sided and are considered statistically significant at a value of less than 0.05. We used SAS (version 9.2) for all statistical analyses.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN 13366390.

### Role of the funding source

Neither the funders or sponsors of the trial participated in study design, in data accrual or analysis, or in the preparation of this paper. Access to the raw data was available to the statisticians (AM, JAD). The corresponding author had full access to all of the data and the final responsibility to submit for publication.

### Results

Between April 21, 2008, and April 26, 2012, we recruited 168 patients (appendix), allocating 84 patients to each trial group (figure 1). Baseline characteristics were much the same between treatment groups (table 1; appendix). After randomisation, eight patients (four in each group) were deemed ineligible because they did not have documented disease progression within 6 months of previous chemotherapy (n=3) or unsatisfactory blood results (n=5). These patients all went on to receive the allocated treatment and were included in the analyses on an intention-to-treat basis.

255 treatment cycles were administered to the 84 patients in the docetaxel group, with a median of three treatment cycles (IQR 1–5) per patient. In the docetaxel group, 19 (23%) of these 84 patients completed all six cycles of treatment, 17 (20%) received only one cycle, and seven (8%) had no docetaxel. Of the 65 patients who did not complete all six cycles, the three main reasons for early discontinuation of treatment were progressive disease in 26 (40%) patients, unacceptable toxicity in 20 (31%) patients, and death in ten (15%) patients. Treatment delays were infrequent (occurring in 29 [11%] of 255 cycles) and were mainly due to toxicity (in ten [34%] cycles), administrative decisions (in eight [28%]), clinical decision (in six [21%]), or patient request (in three

[10%]). The treatment dose was reduced in 23 (27%) patients for a total of 57 (22%) cycles. The overall median course dose intensity was 46% (IQR 19–74).

In the active symptom control group, 30 (36%) of 84 patients completed at least 18 weeks of follow-up. The main reason for early discontinuation of follow-up was death (in 32 [59%] patients).

	Docetaxel (n=84)	Active symptom control (n=84)
Sex		
Male	69 (82%)	67 (80%)
Female	15 (18%)	17 (20%)
Age in years		
Individuals older than 70 years	23 (27%)	16 (19%)
Eastern Cooperative Oncology Group performance status		
0	24 (28%)	22 (26%)
1	46 (55%)	50 (60%)
2	14 (17%)	12 (14%)
Disease status		
Locally advanced	11 (13%)	10 (12%)
Metastatic disease	73 (87%)	74 (88%)
Site of primary disease		
Oesophagus	18 (22%)	15 (18%)
Oesophagogastric junction	27 (32%)	32 (38%)
Stomach	39 (46%)	37 (44%)
Time between end of previous chemotherapy and documented disease progression		
During treatment	36 (43%)	36 (43%)
Within 3 months	27 (32%)	22 (26%)
3–6 months	21 (25%)	26* (31%)

Data are n (%) or median (range). \*Three patients were subsequently shown to have longer than 6 months between end of previous chemotherapy and documented disease progression.

Table 1: Baseline characteristics

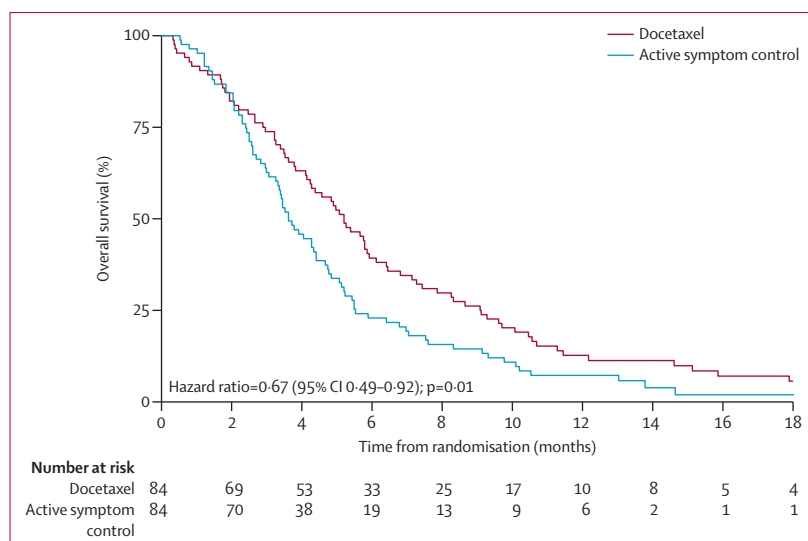


Figure 2: Kaplan-Meier plot of overall survival

16 patients in the active symptom control group went on to have further systemic cancer treatment: 11 entered early phase clinical studies and five had conventional chemotherapy. Seven patients in the docetaxel group went on to have further systemic cancer treatment: three entered early phase clinical trials and four received conventional chemotherapy.

At the time of the planned final analysis, 6 months after we allocated the final patient to treatment, 161 (96%) patients had died (80 patients [95%] in the docetaxel group and 81 [96%] in the active symptom control group). Median follow-up was 12 months (IQR 10–21); one patient in the control group was lost to follow-up after 18 days. Median overall survival for patients allocated to docetaxel was 5.2 months (95% CI 4.1–5.9) compared with 3.6 months (3.3–4.4) for patients in the control group (hazard ratio 0.67, 95% CI 0.49–0.92,  $p=0.01$ ; figure 2). Overall survival in the docetaxel group was 82% (95% CI 72–89) at 2 months and 39% (29–50) at 6 months, and in the control group was 84% (75–91) at 2 months and 23% (15–34) at 6 months. We estimated the number

of patients needed to treat at 6 months to be seven (95% CI 3.9–34.8)—ie, seven patients would be needed to be treated with docetaxel to lead to one extra survivor at 6 months.

A multivariate Cox proportional hazard model showed that performance status ( $p=0.001$ ) and disease status (locally advanced better than metastatic disease, hazard ratio 2.07, 95% CI 1.23–3.50;  $p=0.006$ ) were predictors of overall survival (appendix). Patients with a performance status of 0 had better overall survival than those with a performance status of 1 (hazard ratio 2.00, 95% CI 1.35–2.96) or two (2.16, 1.27–3.66). Disease site ( $p=0.58$ ) and time of progression ( $p=0.58$ ) were not statistically significant predictors of overall survival. The treatment effect remained statistically significant in the multivariate analysis after adjustment for stratification variables ( $p=0.03$ ).

We detected a benefit of docetaxel treatment after stratifying by performance status, disease status, site of disease, and time between end of previous chemotherapy and documented disease progression (figure 3). We saw

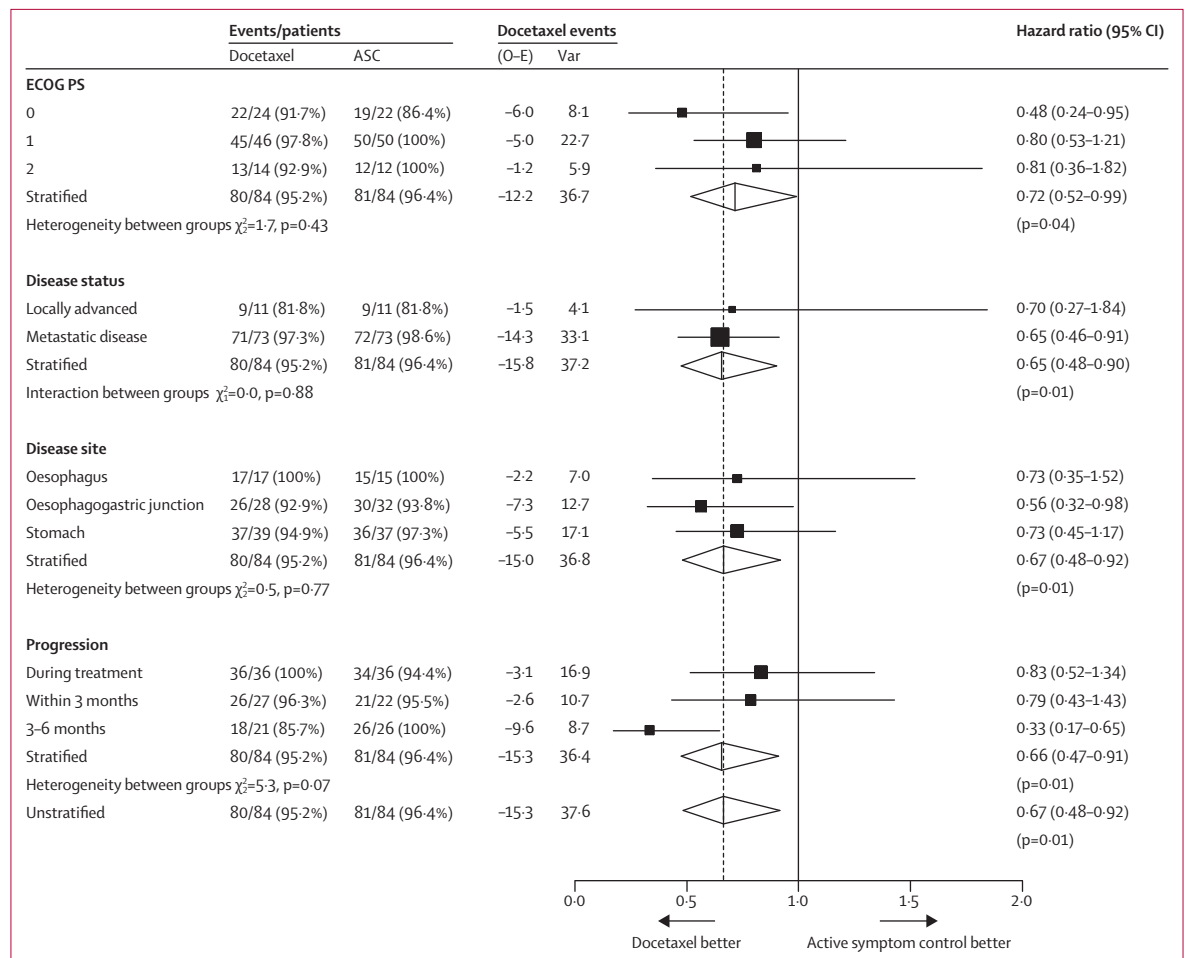


Figure 3: Hazard ratio plot of the treatment effect by prognostic factors for overall survival  
ECOG PS=Eastern Cooperative Oncology Group performance status.

	Docetaxel (n=81)				Active symptom control (n=74)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia without fever	1 (1%)	0	4 (5%)	8 (10%)	0	0	0	0
Anaemia	8 (10%)	10 (12%)	3 (4%)	2 (2%)	7 (9%)	6 (8%)	3 (4%)	1 (1%)
Other blood or bone marrow	7 (9%)	0	2 (2%)	0	3 (4%)	1 (1%)	1 (1%)	1 (1%)
Infection without neutropenia	1 (1%)	8 (10%)	9 (11%)	3 (4%)	5 (7%)	8 (11%)	2 (3%)	0
Febrile neutropenia	0	0	5 (6%)	1 (1%)	0	0	0	0
Constitutional symptoms	16 (20%)	26 (32%)	13 (16%)	0	11 (15%)	14 (19%)	10 (14%)	0
Gastrointestinal	20 (25%)	28 (35%)	21 (26%)	0	18 (24%)	24 (32%)	18 (24%)	0
Haemorrhage or bleeding	4 (5%)	3 (4%)	0	1 (1%)	3 (4%)	1 (1%)	4 (5%)	1 (1%)
Metabolic or laboratory	7 (9%)	7 (9%)	5 (6%)	0	6 (8%)	5 (7%)	3 (4%)	0
Musculoskeletal or soft tissue	1 (1%)	3 (4%)	4 (5%)	0	2 (3%)	0	5 (7%)	0
Neurology	11 (14%)	10 (12%)	3 (4%)	0	10 (14%)	1 (1%)	3 (4%)	0
Pain	17 (21%)	19 (23%)	7 (9%)	2 (2%)	14 (19%)	26 (35%)	15 (20%)	0
Pulmonary or upper respiratory	12 (15%)	6 (7%)	3 (4%)	2 (2%)	8 (11%)	6 (8%)	5 (7%)	0
Allergy or immunological	2 (2%)	3 (4%)	1 (1%)	1 (1%)	1 (1%)	0	0	0
Lymphatic	3 (4%)	3 (4%)	0	0	1 (1%)	1 (1%)	1 (1%)	0
Visual	2 (2%)	1 (1%)	1 (1%)	0	1 (1%)	0	0	0
Renal or genitourinary	1 (1%)	0	1 (1%)	0	0	0	0	0
Vascular	1 (1%)	0	1 (1%)	0	0	0	0	0
Dermatological	22 (27%)	12 (15%)	0	0	12 (16%)	0	0	0

Data are n (%) for the worst grade experienced for each adverse event listed.

Table 2: Adverse events

no statistically significant heterogeneity between the subgroups of each of these factors (figure 3).

For the 56 patients in the docetaxel group assessable for response, best response to treatment was partial response in four (7%) patients, stable disease in 26 (46%) patients, and progressive disease in 24 (43%) patients. Response data were unavailable in two (4%) patients. Median time to progression was 12.2 weeks (95% CI 9.1–18.6) for patients in the docetaxel group. Progression-free survival at 6 weeks was 88% (79–93) and at 24 weeks was 29% (19–38).

Ten deaths (seven in the docetaxel group and three in the active supportive care group) occurred within 30 days of randomisation. Five of the seven patients allocated to docetaxel died before receiving treatment and two deaths were after the first docetaxel cycle. A further three patients died within 30 days of receiving docetaxel. Hence, five (6%) deaths were within 30 days of receiving any docetaxel, but none was attributed to chemotherapy.

More patients in the docetaxel group had one or more grade 4 toxicity compared with those in the control group (17 [21%] patients vs three [4%] patients). Neutropenia, infections, and febrile neutropenia were more common in the docetaxel group versus the control group (table 2). Haemorrhage and pain were more common in the control group than in the docetaxel group (table 2).

560 (69%) of 812 HRQoL forms were returned: 318 (72%) of 442 in the docetaxel group and 242 (65%) of 370 in the active supportive care group (appendix). The main reasons for non-completion of the absent

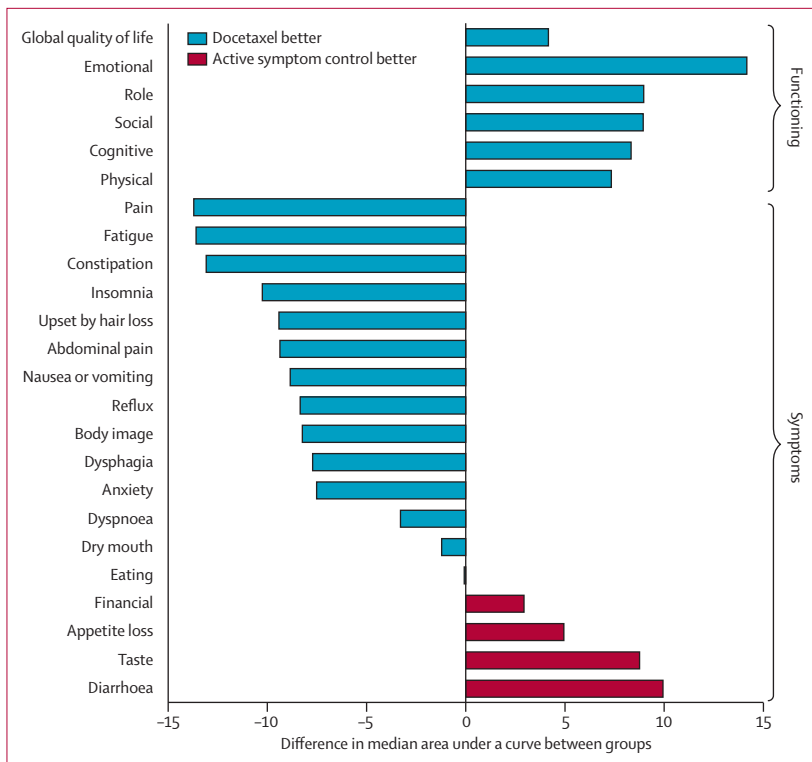
242 on-study HRQoL forms were: administration error (75 [31%] of 242 patients), patient unwell (50 [21%] of 242 patients), or patient refused or did not attend (48 [20%] of 242 patients). By 24 weeks, 118 (70%) patients had died or were off study and no longer participating in HRQoL (51 [61%] patients in the docetaxel group, and 67 [80%] patients in the active supportive care group).

Baseline QLQ-C30 and QLQ-STO22 scores were similar in both groups. Benefits for docetaxel were seen in all pre-specified important domains, of which dysphagia was statistically significant ( $p=0.02$ ), and for several exploratory domains (figure 4).

Patients in the docetaxel group reported less general pain ( $p=0.0008$ ), abdominal pain ( $p=0.01$ ), nausea and vomiting ( $p=0.02$ ), and constipation ( $p=0.02$ ) than those in the control group, but similar global HRQoL ( $p=0.53$ ; appendix). Findings from our sensitivity analysis adjusting for dropouts showed that the mean overall quality-adjusted life weeks over the restricted 24-week reporting period was 12.1 weeks (SD 0.84) for the docetaxel group and 9.3 weeks (0.73) for the control group—docetaxel treatment, therefore, provided on average an extra 2.8 adjusted life weeks compared with active symptom control.

## Discussion

Our findings suggest that, compared with active symptom control, docetaxel improves survival with no adverse effects on global HRQoL and improvement in some HRQoL symptom domains in patients with



**Figure 4: Health-related quality of life (HRQL) outcomes.**

Positive values in function scale and negative values for the symptom scale denote benefit from docetaxel compared with active symptom control.

oesophagogastric adenocarcinoma whose disease has progressed after first-line treatment with platinum-based and fluoropyrimidine-based chemotherapy.

Previously there was no consensus recommendation for second-line chemotherapy in oesophagogastric adenocarcinoma.<sup>20</sup> However, a comprehensive evidence base is now emerging (panel).<sup>20</sup> Findings from a German trial of 40 patients with advanced oesophagogastric carcinoma randomly allocated to either irinotecan or best supportive care was stopped early due to poor recruitment, but patients treated with irinotecan had a median overall survival of 4.0 months compared with 2.4 months for those given best supportive care (hazard ratio 0.48, 95% CI 0.25–0.92).<sup>12</sup> In another trial, treatment with physician's choice of either irinotecan or docetaxel in 133 patients with advanced gastric cancer resulted in a median overall survival of 5.3 months compared with 3.8 months for 69 patients treated with best supportive care, with equivalent efficacy of the two drugs.<sup>3</sup> The strength of the findings of both trials, however, are limited by the absence of robust HRQoL data, although the German group did note improvements in symptoms with chemotherapy.

Biological agents are also under assessment in this setting. The findings of a phase 3 trial of the mTOR inhibitor everolimus showed no benefit compared with placebo (overall survival 5.4 vs 4.3 months;

$p=0.12$ ).<sup>23</sup> Targeting of angiogenesis might be a more productive avenue of investigation. Findings from a study of 355 patients with gastrooesophageal adenocarcinoma treated in the second-line setting with either placebo or with ramucirumab, an inhibitor of VEGFR-2, showed a survival advantage for ramucirumab with median overall survival of 5.2 months versus 3.8 months (hazard ratio 0.78 [95% CI 0.60–1.00];  $p=0.047$ ).<sup>24</sup> Another group have reported the results of a randomised phase 2 trial comparing apatinib (YN968D1; another VEGFR-2 inhibitor) 850 mg given either as a single or divided dose with placebo.<sup>25</sup> Patients treated with either schedule of apatinib had better overall survival (4.83 months and 4.27 months, respectively, vs 2.5 months for placebo;  $p<0.001$  and  $p=0.0017$ , respectively).<sup>25</sup>

We believe that our findings add several important factors to the present evidence base. The largest previously published trial of chemotherapy was done in an Asian population with gastric cancer only.<sup>3</sup> Therefore, the findings of that trial are not ideally suited to guide treatment outside of Asia because evidence exists that tumour biology differs between people of Asian origin and those of white patients.<sup>26</sup> We know of no other trial that included patients with oesophageal adenocarcinoma in addition to those with oesophagogastric junction and gastric adenocarcinoma. Our findings showed improvement in all sites, although the trial was not powered to show statistical significance for each site individually. The median age of 65 years in our study was more representative of the population seen in clinical practice than in other studies in which the median age was less than 60 years.<sup>3,12</sup> We also included patients with an ECOG performance status of 0–2. The only other trial we know of that included any patients with a performance status of 2 had only four such patients in the treatment group.<sup>12</sup>

The slight survival benefit achieved by administration of toxic chemotherapy necessitates careful assessment of HRQoL, toxicity, and disease-specific symptoms. HRQoL data are important to inform clinical decision making, and to provide patients with information about likely effects of treatment on functional aspects of health and symptoms.<sup>27</sup> Studies that have measured HRQoL in gastric cancer often have incomplete datasets or poor reporting, which limits their application. We know of no other study to report comprehensive HRQoL assessment in second-line treatment of advanced oesophagogastric cancer according to the CONSORT PRO guidelines.<sup>28</sup> Our data show that the survival advantage associated with docetaxel treatment also has HRQoL benefits; in particular, pain scores are improved with the intervention. This finding is in keeping with other research showing the predictive value of self-reported pain and survival in oesophagogastric cancer.<sup>29</sup> Unfortunately, however, the health of this population of patients deteriorates rapidly, meaning that questionnaire return is often problematic—our study was no exception, with only 57% of questionnaires returned in



the active symptom control group at 6 weeks. Such low questionnaire return is a limitation of the study, and might in part explain why dysphagia was the only prespecified endpoint to show a benefit in favour of docetaxel. Undertaking home visits might be the only way to improve response to HRQoL surveys in such trials.<sup>30</sup>

We did not measure time to progression in the active symptom control group. In a population with known progressive disease at study entry the value of measuring time to progression in a population not receiving cancer treatment is questionable, and we felt that it was not appropriate to subject these patients to additional unnecessary investigations. The study was planned on the basis that the endpoints to drive change in practice would be overall survival and HRQoL. Patients in both arms of the trial were allowed to receive other treatments after study completion, and a greater number did so in the control group (16 patients) than the docetaxel group (seven patients). If anything, this disparity might be expected to improve outcomes in the control group, and reduce the recorded benefit of docetaxel.

There are areas of possible bias in this trial, principally the open-label design without placebo control (which was felt to be unavoidable given the very obvious toxicities of docetaxel such as alopecia and the ethical difficulty associated with a placebo infusion). The sex ratio in the trial (81% male) is higher than would be expected for the UK oesophagogastric cancer population, generally, in which where the male-to-female ratio is about 65 men to 35 women. The reasons for this high proportion of men are not clear.

Patients in the docetaxel group received steroids with each infusion, which has some potential to bias the HRQoL scores, as does the rate of non-completion of questionnaires. Additionally, although active symptom control was provided for all patients in the trial, and included access to community palliative care and hospice services, we could not standardise the type of active supportive care fully, which is another potential source of bias. This possible bias was mitigated by the fact that patients continued to have regular review at the treating centre, with only one patient in the control group lost to follow-up.

The evidence for improvement in HRQoL with docetaxel, particularly reduced pain, and the survival gain are both consistent with a beneficial effect from chemotherapy. Our findings show that the toxicity of chemotherapy is more than compensated for by gains in symptom control, with no deterioration in global function.

Future clinical trials are needed to further improve outcome in this globally common cancer. Our findings have shown that it is possible to gather and report informative HRQoL data in this poor-prognosis group. Future trials, which should include HRQoL outcome measures, should focus on optimising chemotherapy and the addition of relevant biological agents.

### Panel: Research in context

#### Systematic review

We identified a systematic review of second-line chemotherapy versus supportive cancer treatment in advanced gastric cancers<sup>21</sup> that searched the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 1, 2013), Medline (1950 to March week 4, 2013), and EMBASE (1980 to 2013, week 13) for articles that included the following terms “gastric or gastroesophageal or gastroesophagus or esophagogastric or stomach”, “cancer or neoplasm or carcinoma or malignant or malignancy”, “second line or salvage or supportive care”, “chemotherapy or chemotherapeutic or antineoplastic agent”, and “randomized or randomised, controlled trial or randomised”, and searched the reference lists of relevant articles and reviews and used the related articles feature in PubMed to identify additional articles. The investigators also searched all abstracts from American Society of Clinical Oncology conferences held between 2004 and 2013 and sought expert opinion to identify relevant but unpublished studies. These authors assessed all potentially eligible studies identified by the above search strategy. Clinical trials that met the following criteria were included in the meta-analysis: trials comparing second-line or salvage treatment chemotherapy with best supportive care, and prospective phase 3 randomised trials. The investigators<sup>21</sup> did a meta-analysis of the three high-quality randomised trials identified (including the initial report of our trial, presented at the American Society of Clinical Oncology annual meeting in Chicago, IL, USA, held on May 31 to June 4, 2013), and reported a reduction in the risk of death with second-line chemotherapy with no differences in treatment effect between docetaxel and irinotecan. They also noted that our trial was the only one to address quality of life. The methodology for the systemic review was robust, although the meta-analysis was limited by the absence of patient-level data. However, the findings are lent support by another trial that reported no difference between outcomes for patients treated with either paclitaxel or irinotecan<sup>22</sup> and are the best available assessment of the evidence in this subject area.

#### Interpretation

The results of our trial and others provide level A evidence that second-line chemotherapy can provide both survival and quality-of-life benefits to selected patients who have progressed after first-line treatment for oesophagogastric adenocarcinoma. Docetaxel, paclitaxel, and irinotecan have all shown activity and can be regarded as appropriate for use as second-line treatment, with this study providing new evidence of quality-of-life benefit with docetaxel. All fit patients who progress after first-line treatment should therefore be considered for second-line chemotherapy. In practice, patients who have received a taxane as part of their primary treatment are likely to be treated with irinotecan, whereas those who have not could be considered for either second-line irinotecan or taxane therapy. The role of biological agents such as ramucirumab and apatinib will depend on the results of future trials and regulatory approval, but addition of these agents could prove to add benefit to that already seen with chemotherapy.

On the basis of our findings, we believe that chemotherapy should be offered to fit patients for the second-line treatment of oesophagogastric adenocarcinoma, and that treatment with docetaxel can improve some aspects of quality of life for patients.

#### Contributors

HERF was the chief investigator and did the trial design, trial management, and paper preparation. AM was the trial statistician and did the trial design, preparation of study reports, and preparation of paper including figures, and was a member of trial management group and trial steering committee. JAB, FYC, JW, WM, DF, SM, GWM, DS, SF, IC, and DC recruited patients. JW was a member of the trial steering committee. DC advised on trial design and support the funding process. PK did trial coordination, prepared study reports, and was responsible for pharmacovigilance. NC designed the trial and prepared the submissions for regulatory approval. JMB designed the trial, led HRQoL

assessments, and was a member of the trial management group. JAD designed the trial and was the chief statistician, a member of the trial management group, and a member of the trial steering committee. TJ prepared the first draft of the paper.

#### Conflicts of interest

HERF received research funding from Sanofi. DC received research funding from Roche, Amgen, Celgene, Sanofi, Merck Serono Novartis, and AstraZeneca. JAB received honoraria from Sanofi. IC received research funding and honoraria from Sanofi and consultancy from Sanofi and Lilly Oncology. All other authors declare that they have no conflicts of interest.

#### Acknowledgments

This research was supported by the Cambridge Clinical Trials Unit (CCTU). The COUGAR-02 trial was an academic, investigator-led study. The trial was sponsored by Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK) and funded by Cancer Research UK [grant number C21276/A12372], clinical trial number CRUK/07/013. Sanofi provided and distributed docetaxel to investigators free of charge. HERF was part funded by the National Institute for Health Research Cambridge Biomedical Research Centre. JAB is partly supported by the University College London Hospitals and University College London Comprehensive Biomedical Research Centre. TJ is funded by the Wellcome Trust Translational Medicine and Therapeutics programme. DC is funded by the NIHR Biomedical Centre at the Royal Marsden Hospital and Institute of Cancer Research.

#### References

- 1 Ferlay J, Shin H-R, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893–917.
- 2 Hartgrink HH, Jansen EPM, Van Grieken NCT, Van de Velde CJH. Gastric Cancer. *Lancet* 2009; **374**: 477–90.
- 3 Kang JH, Lee S, Lim DH, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *J Clin Oncol* 2012; **30**: 1513–18.
- 4 Assersohn L, Brown G, Cunningham D, et al. Phase II study of irinotecan and 5-fluorouracil/leucovorin in patients with primary refractory or relapsed advanced oesophageal and gastric carcinoma. *Ann Oncol* 2004; **5**: 64–69.
- 5 Giuliani F, Gebbia V, De Vita F, et al. Docetaxel as salvage therapy in advanced gastric cancer: a phase II study of the Gruppo Oncologico Italia Meridionale (G.O.I.M.). *Anticancer Res* 2003; **23**: 4219–22.
- 6 Jo JC, Lee JL, Ryu MH, et al. Docetaxel monotherapy as a second-line treatment after failure of fluoropyrimidine and platinum in advanced gastric cancer: experience of 154 patients with prognostic factor analysis. *Jpn J Clin Oncol* 2007; **37**: 936–41.
- 7 Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649–55.
- 8 Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**: 365–76.
- 9 Blazeby JM, Conroy T, Bottomley A, et al. Clinical and psychometric validation of a questionnaire module, the EORTC QLQ-STO 22, to assess quality of life in patients with gastric cancer. *Eur J Cancer* 2004; **40**: 2260–68.
- 10 Vickery CW, Blazeby JM, Conroy T, et al. Development of an EORTC Disease Specific Quality of Life Module for use in Patients with Gastric Cancer. *Eur J Cancer* 2001; **37**: 966–71.
- 11 Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000; **92**: 205–16.
- 12 Thuss-Patience PC, Kretzschmar A, Bichev D, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer—a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 2011; **47**: 2306–14.
- 13 Schoenfeld DA, Richter JR. Nomograms for calculating the number of patients needed for a clinical trial with survival as an endpoint. *Biometrics* 1982; **38**: 163–70.
- 14 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
- 15 Cox DR. Regression models and lifetables. *J R Stat Soc [B]* 1972; **34**: 187–220.
- 16 Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Vol. 1. Worldwide evidence 1985–1990. Oxford: Oxford University Press, 1990.
- 17 Qian W, Parmar MK, Sambrook RJ, Fayers PM, Girling DJ, Stephens RJ. Analysis of messy longitudinal data from a randomized clinical trial. MRC Lung Cancer Working Party. *Stat Med* 2000; **19**: 2657–74.
- 18 Fayers PM, Aaronson NK, Bjordal K, et al. *The EORTC QLQ-C30 Scoring Manual (3rd Edition)*. Brussels: European Organisation for Research and Treatment of Cancer, 2001.
- 19 Billingham LJ, Abrams KR. Simultaneous analysis of quality of life and survival data. *Stat Methods Med Res* 2002; **11**: 25–48.
- 20 Okines A, Verheij M, Allum W, Cunningham D, Cervantes A. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** (suppl 5): 50–54.
- 21 Kim HS, Kim HJ, Kim SY, et al. Second line chemotherapy versus supportive cancer treatment in advanced gastric cancer: a meta-analysis. *Ann Oncol* 2013 **24**: 2850–54.
- 22 Hironaka S, Ueda S, Yasui H, et al. Randomized open-label phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 Trial. *J Clin Oncol* 2013; published online Nov 4. DOI:10.1200/JCO.2012.48.5805.
- 23 Ohtsu A, Ajani JA, Bai YX, et al. Everolimus for previously treated advanced gastric cancer: Results of the randomized, double blind, phase III GRANITE-1 study. *J Clin Oncol* 2013; **31**: 3935–43.
- 24 Fuchs CS, Tomasek J, Cho JY, et al. Ramucicirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2013; published online Oct 3. [http://dx.doi.org/10.1016/S0140-6736\(13\)61719-5](http://dx.doi.org/10.1016/S0140-6736(13)61719-5).
- 25 Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol* 2013; **31**: 3219–25.
- 26 Kim J, Sun C-L, Mailey B, et al. Race and ethnicity correlate with survival in patients with gastric adenocarcinoma. *Ann Oncol* 2010; **21**: 152–60.
- 27 Brundage M, Feldman-Stewart D, Leis A et al. Communicating quality of life information to cancer patients: a study of six presentation formats. *J Clin Oncol* 2005; **23**: 6949–56.
- 28 Calvert M, Blazeby JM, Altman DG, Revicki DA, Moher D, Brundage M. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA* 2013; **309**: 814–11.
- 29 Quinten C, Maringwa J, Gotay CC, et al. Patient self-reports of symptoms and clinician ratings as predictors of overall cancer survival. *J Natl Cancer Inst* 2011; **103**: 1851–58.
- 30 Blazeby JM, Nicklin J, Brookes ST, Winstone K, Alderson D. Feasibility of quality of life assessment in patients with upper gastrointestinal tract cancer. *Br J Cancer* 2003; **89**: 497–501.