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

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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/m² 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.
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); 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. 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/m² 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 1·5×10⁹ cells per L or platelet count was above 100×10⁹ per L then treatment was continued at full dose. If a patient’s ANC was below 1·5×10⁹ cells per L treatment was delayed until recovery. If ANC recovered to greater than 1·5×10⁹ 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 0·5×10⁹ cells per L for more than 7 days) or febrile neutropenia, in which case the dose of docetaxel was reduced to 55 mg/m² 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 100×10⁹ per L then treatment was delayed until recovery. If the platelet count recovered to greater than 100×10⁹ 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 50×10⁹ per L, in which
case the dose of docetaxel was reduced to 55 mg/m² 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/m² 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/m² 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/m² of body-surface area for subsequent cycles.

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.13

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.15 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).11

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.15
compared survival differences using a Cox proportional hazard model and calculated hazard ratios with 95% CIs. 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.

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. We handled missing questionnaire data by calculating the scale score if at least half of items were answered. We did sensitivity analyses adjusting for dropouts due to death using a quality-adjusted survival analysis for the global HRQoL score.

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).

Table 1: Baseline characteristics

|                          | Docetaxel (n=84) | Active symptom control (n=84) |
|--------------------------|------------------|------------------------------|
| Sex                      |                  |                              |
| Male                     | 69 (82%)        | 67 (80%)                     |
| Female                   | 15 (18%)        | 17 (20%)                     |
| Age in years             |                  |                              |
| 65 (28–84)               | 66 (36–84)      |
| 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%)                    |

*Three patients were subsequently shown to have longer than 6 months between end of previous chemotherapy and documented disease progression.

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
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).

Table 2: Adverse events

| Adverse event                                      | Docetaxel (n=81) | Active symptom control (n=74) |
|----------------------------------------------------|------------------|-------------------------------|
| **Neutropenia without fever**                      |                  |                               |
| Grade 1                                            | 1 (1%)           | 0                             |
| Grade 2                                            | 0                | 0                             |
| Grade 3                                            | 4 (5%)           | 0                             |
| Grade 4                                            | 8 (10%)          | 0                             |
| **Anaemia**                                        |                  |                               |
| Grade 1                                            | 8 (10%)          | 0                             |
| Grade 2                                            | 10 (12%)         | 0                             |
| Grade 3                                            | 3 (4%)           | 2 (2%)                        |
| Grade 4                                            | 2 (2%)           | 1 (1%)                        |
| **Other blood or bone marrow**                     |                  |                               |
| Grade 1                                            | 7 (9%)           | 0                             |
| Grade 2                                            | 0                | 2 (2%)                        |
| Grade 3                                            | 2 (2%)           | 0                             |
| Grade 4                                            | 0                | 3 (4%)                        |
| **Infection without neutropenia**                  | 1 (1%)           | 0                             |
| **Febrile neutropenia**                            |                  |                               |
| Grade 1                                            | 1 (1%)           | 0                             |
| Grade 2                                            | 8 (10%)          | 0                             |
| Grade 3                                            | 9 (11%)          | 1 (1%)                        |
| Grade 4                                            | 3 (4%)           | 1 (1%)                        |

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

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

| Global quality of life | Docetaxel better | Active symptom control better |
|------------------------|------------------|-------------------------------|
| Emotional              |                  |                               |
| Role                   |                  |                               |
| Social                 |                  |                               |
| Cognitive              |                  |                               |
| Physical               |                  |                               |
| Pain                   |                  |                               |
| Fatigue                |                  |                               |
| Constipation           |                  |                               |
| Insomnia               |                  |                               |
| Upset by hair loss     |                  |                               |
| Abdominal pain         |                  |                               |
| Nausea or vomiting     |                  |                               |
| Reflux                 |                  |                               |
| Body image             |                  |                               |
| Dysphagia              |                  |                               |
| Anxiety                |                  |                               |
| Dyspnea                |                  |                               |
| Dry mouth              |                  |                               |
| Eating                 |                  |                               |
| Financial              |                  |                               |
| Appetite loss          |                  |                               |
| Taste                  |                  |                               |
| Diarrhoea              |                  |                               |

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. 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. 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. 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.

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. 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. 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. 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.30

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.

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. Argenz, Cegene, 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.

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