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Gefitinib for oesophageal cancer progressing after chemotherapy (COG): a phase 3, multicentre, double-blind, placebo-controlled randomised trial — Source link

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Abstract: Background
There is limited evidence on the effectiveness of therapies for oesophageal cancer progressing after chemotherapy and no randomised trials. This phase III study compared gefitinib to placebo in previously treated advanced oesophageal cancer.
Methods
Patients with advanced oesophageal cancer progressing after chemotherapy were randomised (1:1) to gefitinib or placebo, with patients, clinicians and trial office staff blinded to treatment allocation. Treatment continued until disease progression, unacceptable toxicity or patient choice. Outcomes: primary: overall survival (OS); Secondary: patient reported outcomes (PROs) (pre-specified: quality of life, dysphagia, eating restrictions and odynophagia); progression free survival (PFS) and safety.
Findings
450 patients (median age 64*1 years; 83% male) were randomised. There was no difference in OS (median: gefitinib 3*73 versus 3*67months; hazard ratio=0*90; 95%CI: 0*74, 1*09; p=0*29). Amongst the pre-specified PROs, odynophagia was significantly better in the intervention group (adjusted mean difference -8*61; 95%CI: -14*5, -2*7; n=312; p=0*004) and other PROs showed consistent improvement. Gefitinib increased median PFS from 1*17 to 1*57months, (hazard ratio, 0*80; 95%CI: 0*66, 0*96, p=0*020). Gefitinib was well tolerated with diarrhoea being the commonest toxicity, gefitinib: 5*8% versus 0*9%. Disease control rate at eight weeks was gefitinib 24*1% versus 15*6% (p=0*023), with observed responses occurring rapidly and lasting 1.17-7.33 months.
Interpretation

The use of gefitinib as a second line treatment in oesophageal cancer in unselected patients does not improve overall survival, but has palliative benefits in subgroup of these difficult-to-treat patients with limited life expectancy. Future research should focus on identification of predictive biomarkers to identify this subgroup of benefiting patients.

Funding
The study was funded by Cancer Research UK. Gefitinib and matching placebo were supplied free of charge by AstraZeneca as 250mg tablets.
Trial registration: ISRCTN: 29580179

Gefitinib for oesophageal cancer progressing after chemotherapy: a phase III, multicentre, double-blind, placebo-controlled randomised clinical trial (COG)

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Introduction

Oesophageal cancer is the 6th commonest cause of cancer death in the world.[1] Clinical outcomes are poor, with 5 year survival only 10 to 15%, and the majority of patients presenting with advanced disease[2]. In the western hemisphere there has been a dramatic rise in the incidence of adenocarcinoma in the last 25 years associated with increasing body mass index.[3] In the other parts of the world squamous cell cancers dominate and are increasing rapidly in incidence in Japan, India, China, and Africa associated with increased smoking.[4]

Accordingly, treatment of oesophageal cancer is largely palliative in intent [5]. In advanced oesophageal cancer first line treatment with cisplatin or oxaliplatin combined with 5FU or capecitabine can improve survival.[6] Adding epirubicin and taxanes may offer some additional benefit, and in HER2 positive patients addition of trastuzumab improves survival.[7] For squamous cell cancer mitomycin combined with ifosfamide and cisplatin is active.[8] When progression occurs, the role of second line chemotherapy is controversial with only limited data regarding clinical effectiveness[9]. There are no randomised phase III trials of second line chemotherapy in either adenocarcinoma or squamous cell carcinomas of the oesophagus and there is a lack of well-designed and conducted studies in second line chemotherapy with patient reported outcomes (PROs) which are important in decision-making when life expectancy is poor.

In gastric cancer randomised second line therapy trials have shown survival and PRO benefits for docetaxel, paclitaxel, ramucirumab, ramicurumab plus paclitaxel and irinotecan[10]. There has been a tendency for clinicians to extrapolate this evidence from gastric cancer to the second line treatment of oesophageal cancer. However considering the clinical and biological differences between gastric and

oesophageal cancer, this approach is likely to result in sub-optimal treatment for patients with oesophageal cancer.

EGFR is expressed in the majority of oesophageal cancers and associated with poor survival.[11] Gene copy number changes are common in oesophageal adenocarcinomas relative to other gastrointestinal (GI) tract adenocarcinomas.[12] Increased copy number of the EGFR gene is found in 5-10%, and is associated with poor survival. In addition, activating mutations in exons 18-21 EGFR have been found in oesophageal cancer patients.[13] This provided the rationale for investigation of anti-EGFR therapies in oesophageal cancer and there have been five reported Phase II trials of the EGFR tyrosine kinase inhibitors (TKIs) gefitinib,[14] or erlotinib involving 147 patients with an overall objective response rate of 8·8%. [9] This contrasts to the inactivity of EGFR TKIs in gastric cancer where no responses have been seen in 80 patients in Phase II trials.[15, 16]

Due to this activity of gefitinib in oesophageal cancer after chemotherapy failure, and the data implicating EGFR and its signaling transduction pathway in pathogenesis and prognosis, we designed a multi-centre phase III randomised trial of sufficient statistical power to reliably detect possible benefits in both survival and patient reported outcomes, the latter in order to explore the impact of gefitinib on generic and disease specific aspects of health related quality of life (HRQL). COG (Cancer Oesophagus Gefitinib), is the first randomised trial of systemic therapy in this indication.

Methods

Patients

Eligible patients were adults with histologically confirmed adenocarcinoma, squamous cell carcinoma , poorly differentiated oesophageal cancer or Type I/II Siewert junctional tumours, had up to two prior chemotherapy and one chemo-radiotherapy regimens, WHO performance status 0-2, ability to swallow tablets, no contra-indications to gefitinib, and either measurable or evaluable disease on CT. Patients with brain metastases were considered eligible if they were stable after cranial irradiation at study entry. Patients receiving cytotoxic chemotherapy, immunotherapy or hormonal therapy or who had evidence of clinically active interstitial lung disease or abnormal blood results (by predefined criteria) were excluded.

Randomization and masking

Patients were randomised 1:1 to oral gefitinib 500 mg/day or matching placebo. All patients received best supportive care (BSC), defined as care in accordance with the local practice of each institution. Treatment continued until disease progression, unacceptable toxicity, or patient choice. The protocol provided detailed guidelines for dose interruption (maximum of 14 days) or single dose reduction to 250mg/day for adverse events.

Patients were allocated to the two treatment arms using central computer allocation using simple randomization with permuted blocks with variable block sizes and no stratification factors. Patients, clinicians, local site and trial office staff were blinded to the treatment allocation. Six months after completion of recruitment the blind was broken for the patients remaining on trial medication and patients on the gefitinib were allowed to continue on gefitinib.

Study Design and Treatment

Written informed consent was obtained. The study was conducted in accordance with the protocol, good clinical practice , the Declaration of Helsinki, and was approved by National Research Ethics Service Committee (REC reference: 08/H0505/127). An independent Trial Steering Committee supervised the conduct of the study. An independent Data Safety Monitoring Committee performed biannual safety reviews.

Patients had baseline CT scan of chest, abdomen, and pelvis, repeated at 4 and 8 weeks and then 8 weekly until disease progression. Response was assessed using RECIST version 1.0 by the local investigator. Patients with progressive disease, or stable disease with symptom deterioration discontinued randomised treatment.

The primary outcome was overall survival (OS) defined as time from randomisation until death from any cause with censoring for patients still alive at the end of the study. PFS was defined as time from randomisation until radiological or clinical progression or death from any cause if progression was not previously reported, with censoring for patients alive and progression free at the end of the study. Safety was measured by assessing adverse reactions and toxicities of grade 2-5 for skin toxicity and diarrhoea (known side effects of gefitinib) and grade 3-5 for all other toxicities, using CTCAE v4.0, monitored continuously throughout treatment and up to 30 days post treatment completion.

HRQL was assessed using the generic EORTC QLQ-C30, [17] and the oesophageal, junctional and gastric cancer specific instrument, EORTC QLQ-OG25. [18] The items on both instruments were scaled and scored by using the recommended EORTC procedures.[19]. Questionnaires were self-completed by patients while attending clinic visits at baseline (prior to treatment), 4, 8 and 12 weeks until progression.

Statistical Analysis

The sample size of 450 was estimated to detect an improvement from 10% 1-year survival, as reported by previous Phase II trials[9, 14] to 18% with a power of 82·5%, 2-sided 5% significance allowing for a 10% loss to follow up (HR=0·745, 389 events).

A statistical analysis plan was finalised before the blind was broken and analysis undertaken. An intention-to-treat analysis for survival used Kaplan-Meier survival curves and the log-rank test, with Cox proportional hazards modelling to estimate hazard ratios and 95% confidence intervals. Binary outcomes were compared using the chi-squared test.

To reduce errors from multiple testing, four PROs were pre-specified as of particular importance: global quality of life, dysphagia, eating restrictions and odynophagia. These were assessed at 5% significance while the remaining PROs were assessed as exploratory variables using 1% significance. The PROs were compared using analysis of covariance (ANCOVA) at 4 weeks adjusted for baseline values. This was repeated at 8 and 12 weeks. Response for patients with measureable lesions was assessed by comparing the percentage change (from baseline to 4 weeks) in longest diameter of the target lesions and presented as a waterfall plot. Disease control rate at 8 weeks was defined as where complete or partial response and stable disease observed at 4 weeks was confirmed at the 8 week scan. Post protocol therapy was collected and summarized. Analyses were undertaken using Stata version 12·0 (StataCorp, College Station, TX).

Results

Patient demographics

From 30th March 2009 to 18th November 2011, 450 patients from 48 UK centers were enrolled and randomised to gefitinib (n = 225) or placebo (n = 225) and followed up until death or the end of the study (31May2012). One patient on the gefitinib arm withdrew consent shortly after being randomised and is excluded from all analyses. The CONSORT flowchart (Figure 1), includes numbers of PRO questionnaires completed at each time-point, and the reasons for early discontinuation of treatment

Baseline clinical characteristics and PRO scores were well balanced across treatment groups (Table 1). Patients reported high levels of symptoms (>30) for eating restrictions, fatigue, pain, insomnia, appetite loss, anxiety and weight loss and poor global quality of life (53·5).

Study treatment and safety

Median (range) duration of treatment was 44 days (0 to 680) on gefitinib versus 35 days (0 to 371) for placebo. 210 SAEs occurred in 150 patients, 101 on placebo and 109 on gefitinib (p=0·74). Grade 2-5 toxicities reported in more than 10% of patients in the gefitinib arm were diarrhoea (16·5%), skin toxicity (20·5%) and fatigue (10·7%) (Table 2). Most of the excess toxicities were grade 2 with incidence for grade 3 diarrhoea (5·8%) and skin rash (2·2%), no grade 4 or 5 toxicities were reported. Other toxicities were of low frequency, and similar between the treatment arms. Dose reduction from 500 mg to 250 mg occurred in only 12 patients, 10 on gefitinib.

Overall and Progression free survival

At the end of the study 417 (93%) deaths and 432 (97%) progression events had been observed. There was no difference between the two arms for overall survival, HR=0·90; (95% CI: 0·74, 1·09; log rank test: p= 0·293) (Figure 2A). The estimated median (95%CI) OS was 3·73 months (3·23, 4·50) with gefitinib and 3·67 months (2·97 to 4·37) with placebo. The trial, which did not stratify patients by performance status (PS), showed it was strongly prognostic of survival. When all patients in the trial were analyzed (not separated by treatment) the median OS (95%CI) was PS0=6·1months (4·9, 7·4), PS1=3·9 months (3·2, 4·4), PS2=2.0 (1·6, 2·4) months, p<0·0001 (Figure 2B).

Gefitinib improved PFS with the estimated median PFS (95%CI) gefitinib 1·57 (1·23, 1·90) compared to placebo 1·17 months (1·07, 1·37), HR: 0·80 (95%CI 0·66, 0·96) log rank test p=0·020 (Figure 2C).

Figure 3 shows the waterfall plots for the patients with measureable disease at both baseline and 4 weeks with response confirmed at the 8 week time point. The disease control rate at 8 weeks was 24·1% (48 SD and 6 PR) for gefitinib versus 15·6% (34 SD and 1 PR) for placebo (p=0·023). Disease control rate at 8 weeks was 23·1% for adenocarcinoma and 28·0% for squamous cell carcinoma for patients on gefitinib (p=0.478). When observed, objective responses were rapid, 7 responses were seen at week 4 and only 1 additional response was first recorded at week 8. Responses were durable with a range of 1·17 to 7·33 months.

Only 98 (22%) patients had further therapy once they came off study treatment with no differences between treatment arms (p=0·36).

Patient reported outcomes

Compliance at baseline was 94% (423/449) and remained high at 79% (245/312), 74% (133/180) and 66% (84/127) at 4, 8 and 12 weeks respectively. 1321 (2·7%) individual items were missing from the questionnaires and these were imputed according to EORTC guidelines. [19] Four weeks after start of treatment, 312 (70%) of patients were still alive and progression free. Figure 4 shows the mean raw scores for the pre-specified PRO outcomes over the four time-points.

In total, 231 patients (placebo 121, gefitinib 110) completed both baseline and 4 week questionnaires and could be included in the primary analysis. Global quality of life deteriorated for all patients from baseline to 4 weeks, but less for those on gefitinib. Patients also experienced more dysphagia and eating restrictions at four weeks compared to baseline but in the gefitinib arm these were not as severe as for the placebo group, although this did not reach traditional statistical significance (Table 3). Odynophagia worsened from baseline to 4 weeks for patients on placebo and significantly improved for patients on gefitinib (adjusted mean difference: -8.61, 95%CI -14.49, -2.73, p=0.004) (Table 3).

Other exploratory PRO functions and symptoms were improved (or not worsened) for patients on gefitinib compared to those on placebo. Patients on the gefitinib arm had less deterioration in social

functioning (p=0.013), fewer problems with pain (p=0.035), constipation (p=0.0001), cough (p=0.013) and speech (p=0.0004) (Table 4). Patients on gefitinib, however, reported significantly more diarrhoea (p<0.0001).

Figure 5 presents a profile plot of mean change from baseline to 4 weeks for all functional and symptom scales and single items in both questionnaires. This demonstrates that patients on placebo have deteriorating function and increasing symptoms by 4 weeks, and although the pattern is similar in the gefitinib arm, the degree of deterioration is less, in particular for social function (p=0.013). In the gefitinib arm specific symptoms are palliated: sleep (p=0.136), constipation (p=0.0001), dysphagia (p=0.228), odynophagia (p=0.004), pain and discomfort (p=0.172), anxiety (p=0.096), cough (p=0.013) and speech (p=0.0004).

With reducing numbers at the later time-points there was insufficient power to detect any difference between the treatment arms. Moreover, repeated measures over time did not detect any statistical differences in the four pre-specified domains.

Discussion

COG is the first randomised trial of systemic therapy in oesophageal cancer patients progressing after chemotherapy. The EGFR TKI gefitinib was chosen to test against placebo because of significant activity observed in five previous phase II clinical trials. [9, 14] No predictive biomarkers for gefitinib in oesophageal cancer had been identified so the COG trial could not use biomarkers to stratify or select patients for treatment.

COG showed no overall survival benefit for gefitinib over placebo, but a small significant benefit in PFS and some aspects of HRQL were observed, including an improvement in a pre-specified PRO, odynophagia.

The PFS benefit for gefitinib (HR of 0·80, p=0·020) was observed across most subgroups, including adenocarcinoma, squamous cell cancers, oesophagus and junctional cancers. Similar trends were seen for OS although they did not reach significance. Although, the biological differences between adenocarcinoma and squamous cell carcinoma are increasingly characterised,[20, 21] this does not appear to be significant for treatment with geftinib in the second line setting investigated in this study.

The increased disease control rate, consistent benefit in PROs and PFS may suggest the existence of a gefitinib responsive subgroup of oesophageal cancer patients. Our data suggests that this comprises a minority subgroup of patients who derive clinically significant benefits from geftinib. The observation of rapid and durable objective responses, and prolonged periods of disease control in some gefitinib treated patients further supports this. Identification of a predictive biomarker for this gefitinib responsive subgroup, similar to for example, the use of activating EGFR mutations to select NSCLC patients that benefit from EGFR TKI therapy, would increase the clinical and cost effectiveness of

gefitinib in oesophegal cancer. We are conducting translational research on tumour specimens from COG to identify predictive biomarkers for gefitinib (TRANSCOG study).

As well as TKIs, oesophagogastric cancers have also been treated with anti-EGFR antibodies. Single agent activity is low[22] and investigators have focused on combination with chemotherapy. [23, 24] However, in phase III trials combining anti-EGFR monoclonals with chemotherapy in the first line setting, overall survival was reduced from 11·3 to 8·8 months with panitumumab in months and was reduced from 10·7 to 9·4 months with cetuximab. [23, 24] This has been interpreted as indicating a lack of activity of anti-EGFR therapies in oesphagogastric cancer, however it may be more significant that the addition of either EGFR TKIs or anti-EGFR antibodies to platinum based chemotherapy in a variety of malignancies, notably in NSCLC[25, 26] and colorectal cancer, [27] has not been beneficial, but the use of both anti-EGFR monoclonals in colorectal cancer[28] and TKIs in NSCLC [28] after first line treatment as single agents has shown survival benefit.[29] The finding of anti-tumour activity for gefitinib, in a sub-group of responsive patients in the COG trial could provide a similar consistent observation in oesophageal cancer.

The gefitinib toxicity profile observed in the current study was generally consistent with that previously observed for gefitinib in in other tumour typesr[30] with no new safety signals identified.

Our study has strengths, including detailed examination of the impact of treatment on PROs, and it is the first multi-centre RCT in oesophageal cancer that has included a well-designed comprehensive PRO assessment. However, there are still some limitations, including only patients who had not progressed at four weeks were asked to complete the PRO questionnaires and are included in the analysis. This may have impacted on the results and patients progressing at this time point may have had a different PRO profile because treatment may have been withdrawn earlier due to general deterioration. Skin toxicity is a known side effect of gefitinib and was not directly measured although the global quality of life score reflect problems with skin toxicity, but this did not vary between groups.

In conclusion, the phase III COG study did not meet its primary endpoint of demonstrating a significant overall survival benefit for gefitinib compared with placebo in unselected patients with oesophageal cancer progressing after previous systemic chemotherapy. An increased disease control rate, consistent benefits in PROs and PFS was demonstrated in gefitinib treated patients. Together with the observation of rapid and durable responses and prolonged disease control in a minority of patients treated with gefitinib, this suggests significant anti-tumour activity in an as yet unidentified small gefitinib responsive subgroup. The data presented is valuable for clinical practice and decision-making indicating that without biomarker stratification, gefitinib has marginal clinical benefits in advanced oesophageal cancer, but could be considered in particular for the palliation of specific symptoms. Identification of a predictive biomarker to identify the gefitinib responsive subgroup of oesophageal cancer patients would greatly increase clinical utility and is the priority for ongoing work.

Conflicts of Interest

Prof David Ferry received a grant from AstraZeneca to continue with ongoing research into FRGR inhibitor AZD4547 and money for an educational DVD on EGFR mutation analysis. Dr Russell Petty has received money from AstraZeneca to travel to external meetings and has a current research grant for an unrelated project from the company. Dr Anirban Chatterjee has previously received payment from AstraZeneca for talking about gefitinib at an external meeting. Prof Janusz Jankowski has received payment for board membership and consultancy work from AstraZeneca as well as grants to conduct research at his institution. No other Co-Authors have any Conflicts of Interest. JMB is supported by the MRC ConDuCT-II Hub for Trials Methodology Research

Contributors

DRF was Chief Investigator for the trial. DRF, SJD, RDP, JJ, RK and JMB contributed to the conception and design of the study and drafted the protocol. DRF, SJD, LP, MD, SRP and PJ were involved in the day to day running of the trial. SJD was responsible for all statistical analysis. DRF, RDP, HA, WM, JT, MH, AC, SF, AG-A, DF, RH, AD-S were principle investigators at centres recruiting at least 5% of the patients, and TG is a Research Nurse at one of the sites. In addition JT, DF, SF also sat on the Trial Management Group for the trial. JMB was the Quality of Life Advisor for the trial and was involved in the study design, data analysis and the interpretation and writing of this paper.

DRF, SJD, JMB and RDP were responsible for data analysis interpretation and preparation of this manuscript. All authors have contributed to, seen and approved the final draft.

All authors had full access to all the data in the study and final responsibility for the decision to submit for publication.A full list of all COG study investigators is listed in the appendix.

Role of the funding source

The study was funded by Cancer Research UK and jointly sponsored by the University of Oxford and the Royal Wolverhampton Hospitals NHS Trust. Gefitinib and matching placebo were supplied free of charge by AstraZeneca as 250mg tablets. These parties had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data in the study and final responsibility for the decision to submit for publication.

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Figure 1: CONSORT Flowchart

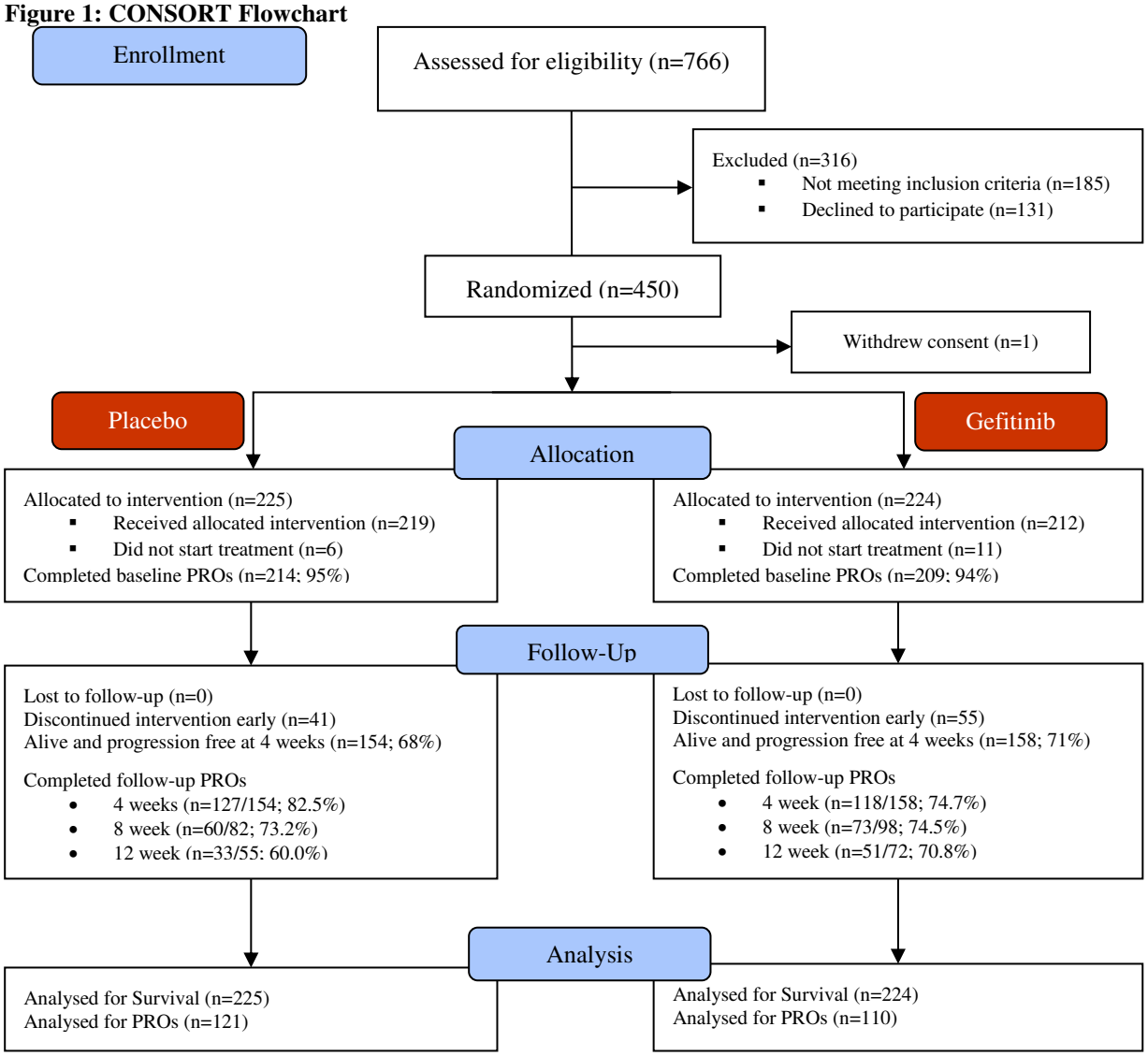


Table 1: Baseline clinical characteristics and PROs

Variable	Placebo N=225	Gefitinib N=224
Clinical Characteristics		
Age at randomisation median (IQR) years	64·9 (58·2, 70·7)	64·7 (58·0, 70·1)
Time since diagnosis median (IQR)n years	0·92 (0·60, 1·47) 216	0·96 (0·62, 1·45) 220
Gender (number (%))		
Male	189 (84·0%)	183 (81·7%)
Female	36 (16·0%)	41 (18·3%)
Original diagnosis (number (%))		
Adenocarcinoma	168 (74·7%)	173 (77.2%)
Squamous cell carcinoma	56 (24·9%)	50 (22·3%)
Undifferentiated	1 (0·4%)	1 (0·4%)
Disease site (number (%))		
Oesophageal	181 (80·4%)	171 (76·3%)
Type I Junctional	21 (9·3%)	26 (11·6%)
Type II Junctional	23 (10·2%)	27 (12·1%)
Performance Status (number (%))		
0	56 (24·9%)	57 (25·5%)
1	125 (55·6%)	117 (52·2%)
2	44 (19·6%)	50 (22·3%)
Prior treatment[a] (number (%))		
None	1	0
One	137 (60·9%)	137 (61·2%)
Two	75 (33·3%)	78 (34·8%)

Three	12 (5·3%)	9 (4·0%)
Brain metastases (number (%))		
No	217 (96·4%)	223 (99·6%)
Yes	8 (3·6%)	1 (0·4%)
BMI mean (SD) n	24·01 (4·77) 212	24·01 (4·94) 214
Pre-specified PROs		
Global quality of life [b, c]	53·5 (21·4) 207	53·5 (22·7) 198
Dysphagia [d, e]	21·5 (23·7) 211	20·9 (24·2) 205
Eating restrictions [d, e]	40·2 (27·1) 211	38·9 (27·4) 204
Odynophagia [d, e]	23·4 (25·0) 210	21·5 (24·4) 203
Exploratory PROs		
Physical Functioning [b, c]	71·7 (24·4) 214	68·0 (23·6) 208
Role functioning [b, c]	63·7 (30·9) 213	57·0 (34·9) 207
Emotional functioning [b, c]	74·7 (22·7) 207	74·1 (23·9) 198
Cognitive functioning [b, c]	84·5 (20·8) 207	80·9 (21·2) 199
Social functioning [b, c]	66·5 (30·8) 207	59·8 (30·9) 198
Fatigue [b, e]	44·4 (27·0) 214	46·0 (25·0) 207
Nausea and vomiting [b, e]	18·7 (23·4) 214	18·9 (24·9) 208
Pain [b, e]	36·7 (29·9) 214	33·8 (29·5) 209
Dyspnoea [b, e]	27·5 (28·1) 212	28·5 (31·5) 207
Insomnia [b, e]	30·5 (30·8) 214	33·8 (32·8) 208
Appetite Loss [b, e]	38·3 (34·5) 213	40·1 (34·2) 207
Constipation [b, e]	28·0 (32·1) 213	31·1 (33·7) 206
Diarrhoea [b, e]	9·4 (20·3) 206	8·9 (18·2) 199
Financial difficulties [b, e]	13·9 (25·9) 206	18·5 (29·7) 198
Reflux [d, e]	22·6 (25·2) 211	21·3 (27·1) 204
Pain and discomfort in stomach area [d, e]	28·2 (28·1) 211	26·9 (27·7)205
Anxiety [d, e]	59·0 (29·2) 211	53·9 (31·8) 205
Eating with others [d, e]	25·5 (34·2) 209	22·4 (31·5) 204
Trouble swallowing saliva [d, e]	9·9 (21·3) 211	11·8 (23·7) 204
Choking [d, e]	9·3 (17·9) 207	10·5 (22·2) 203
Dry mouth [d, e]	26·7 (30·1) 211	30·1 (33·3) 205
Taste [d, e]	23·1 (31·3) 208	28·2 (33·0) 203
Cough [d, e]	28·6 (28·8) 210	32·0 (28·6) 204
Speech [d, e]	10·7 (22·5) 211	11·5 (21·7) 203
Body Image [d, e]	23·4 (34·1) 211	25·1 (32·1) 202
Weight loss [d, e]	35·6 (34·3) 208	36·1 (35·1) 202
Hair loss [d, e]	17·4 (27·5) 117	17·9 (31·4) 108

[a] Patients allowed 1-2 prior chemotherapy and 1 chemoradiotherapy regimen
[b] EORTC QLQ-C30
[c] Global quality of life or functional scales – high score = high level of functioning
[d] EORTC QLQ-OG25
[e] Symptom scales or single items – high score = high level of symptoms or problems

Table 2. Toxicity: Highlighted toxicities by CTCAE v4.0 grade (worst grade per toxicity per patient).

Toxicity (worst CTCAE grade)	Placebo (n=225)				Gefitinib (n=224)			
	2	3	4	5	2	3	4	5
Diarrhoea	4	2	-	-	23	13	-	-
Skin toxicity	1	1	-	-	41	5	-	-
Nausea &/or vomiting		7	-	-		8	-	-
Pain Abdominal		9	2	-		6	1	-
Fatigue		12	1	-		23	1	-
Worst grade any toxicity per patient	3	66	21	3	32	74	21	6

Figure 2. Survival

A. Kaplan-Meier plot of Overall Survival by treatment.
B. Kaplan-Meier plot of OS by performance status.
C. Kaplan-Meier plot of PFS by treatment
Figure 2A: Kaplan Meier-plot of Overall survival by treatment

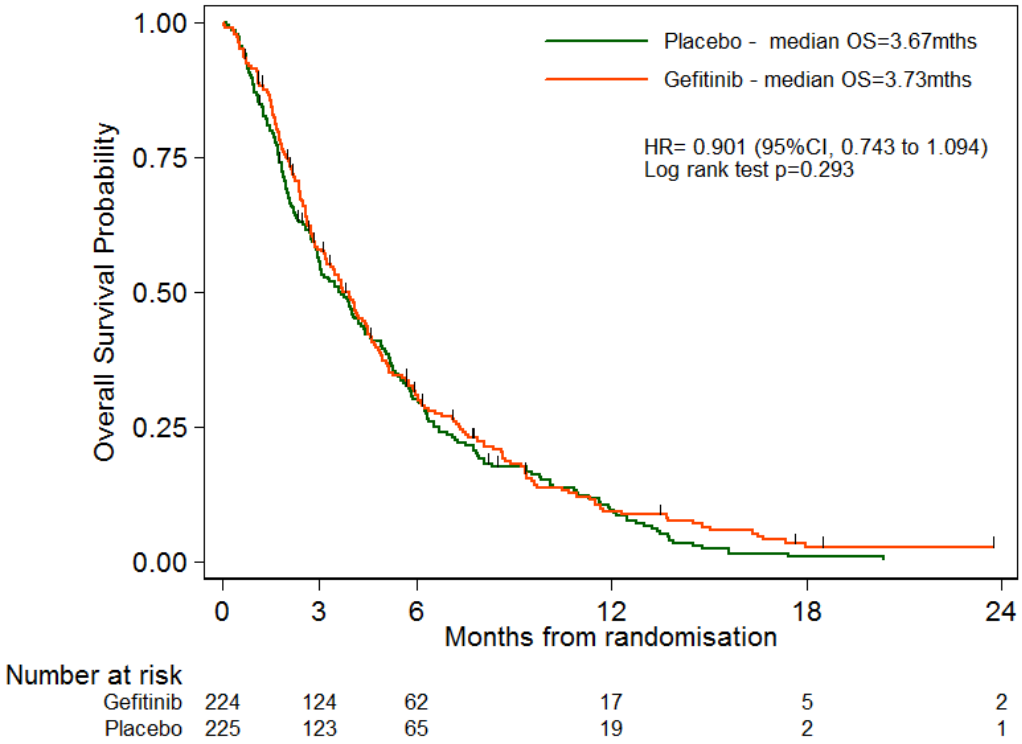


Figure 2B: Kaplan-Meier plot of OS by performance status

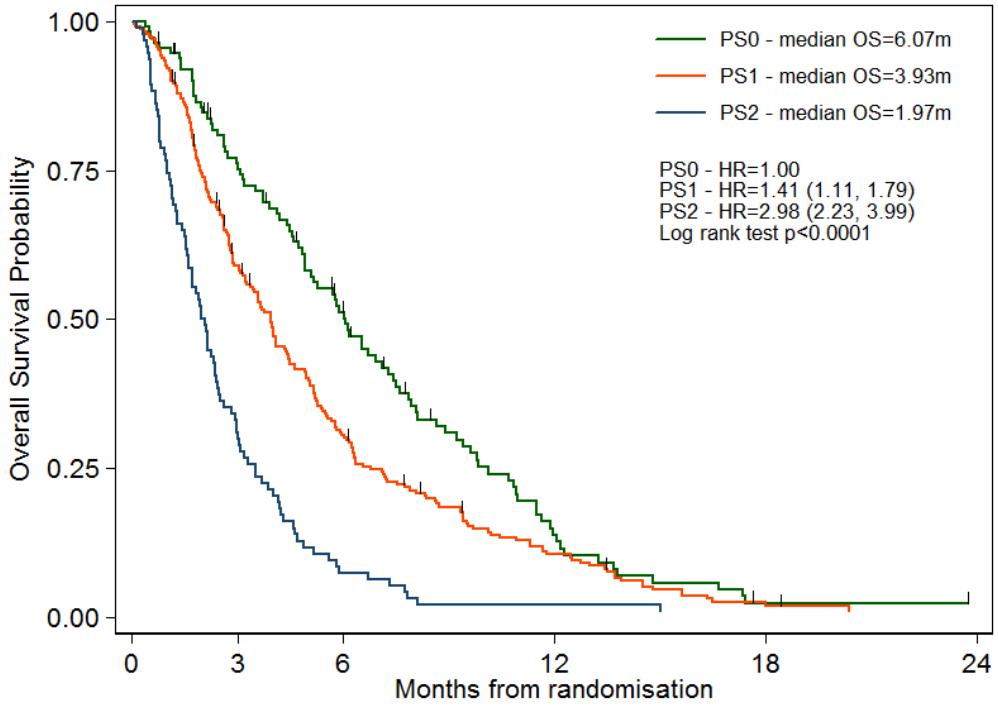


Figure 2C: Kaplan-Meier Plot of PFS by treatment

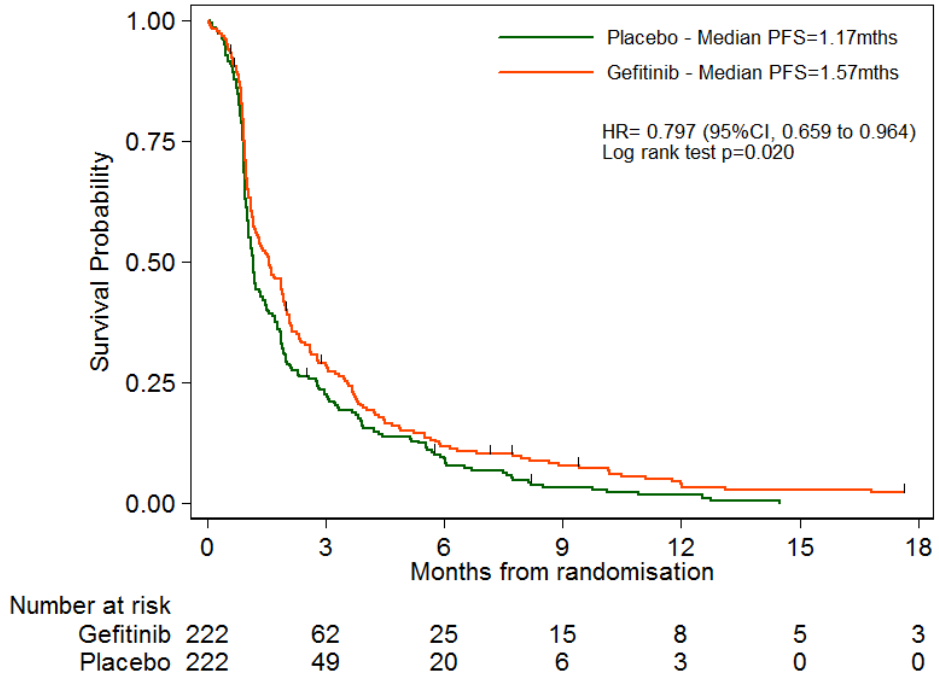
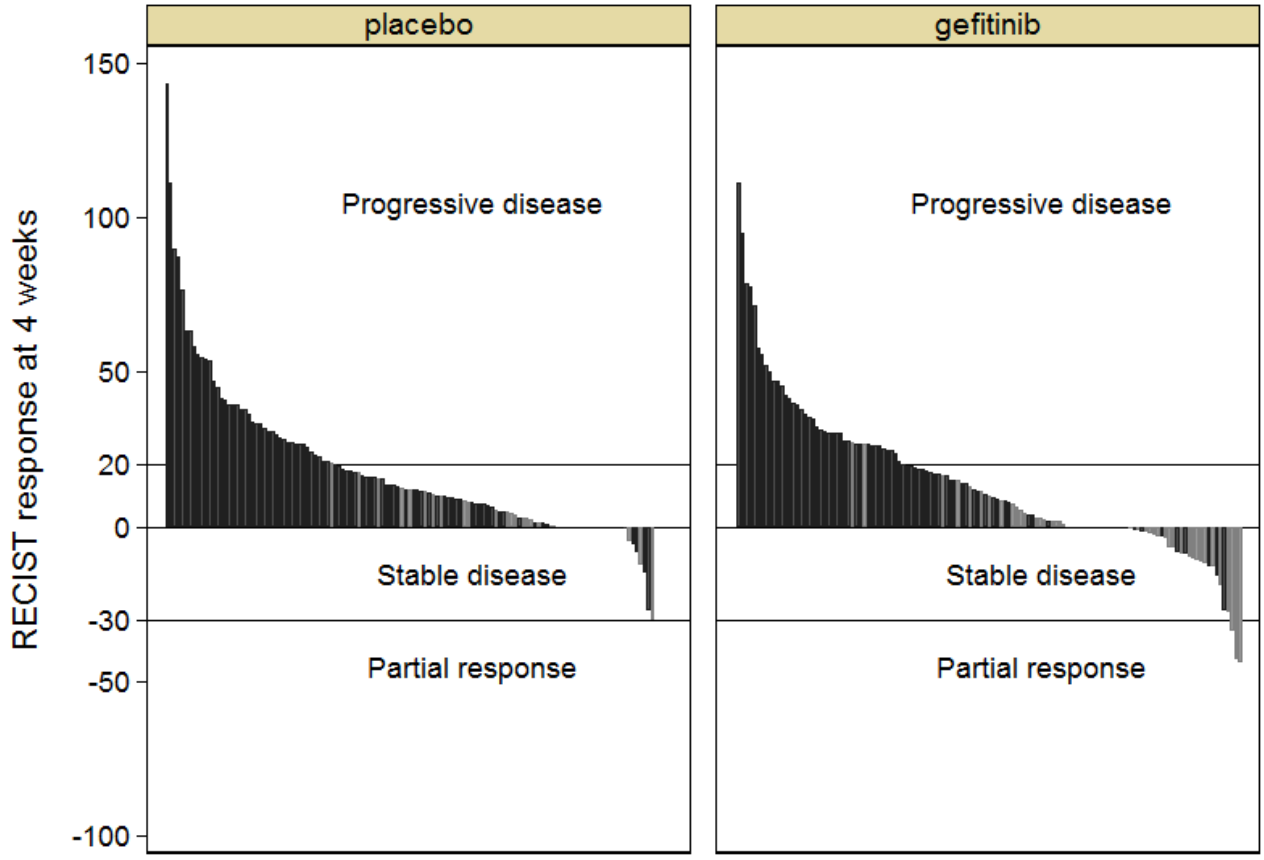
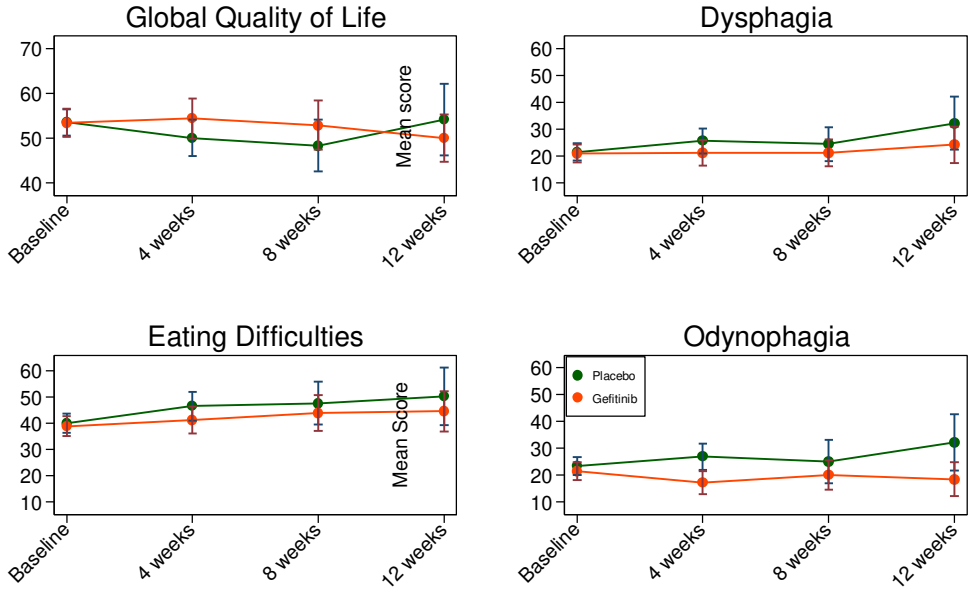


Figure 3. Waterfall plots for patients with measurable disease at baseline and 4 weeks, response confirmed at 8 weeks



Black – recorded as progressed by 8 weeks, may have been new lesions
Grey – not reported as progressed

Figure 4: Mean raw scores for pre-specified PROs at all time-points



Higher score equates to better quality of life or more symptoms
Number of patients per time-point
Placebo: Baseline 214; 4weeks 127; 8weeks 60; 12weeks 33
Gefitinib: Baseline 209; 4weeks 118; 8weeks 73; 12weeks 51

Table 3: Pre-specified PROs -Treatment effect at 4 weeks – analysis by ANCOVA adjusted for baseline values

Outcome of interest	Placebo Adjusted Mean (95%CI) N	Gefitinib Adjusted Mean (95%CI) N	Adjusted mean difference at 4 weeks (95%CI) N	P-value
Global QOL [1]	-6·44 (-9·89, -2·99) 121	-3·75 (-7·36, -0·13) 110	2·69 (-2·33, 7·72) 231	0·293
Dysphagia[2]	5·00 (1·45, 8·55) 121	1·82 (-1·91, 5·55) 110	-3·18 (-8·36, 2·00) 231	0·228
Eating restrictions[2]	7·74 (3·73, 11·75) 120	3·63 (-0·57, 7·84) 109	-4·11 (-9·96, 1·75) 229	0·168
Odynophagia[2]	4·46 (0·43, 8·49) 119	-4·15 (-8·38, 0·08) 108	-8·61 (-14·49, -2·73) 227	0·004

[1] For global quality of life a positive adjusted mean difference implies that patients on gefitinib arm have less deterioration than those on placebo

[2] For the symptom scores a negative adjusted mean differences implies that patients on gefitinib has less deterioration or even improvement of symptoms when compared to those on placebo

Table 4: Treatment effect at 4 weeks for exploratory PRO outcomes after adjusting for baseline HRQL values

Exploratory Outcome of interest	Placebo Adjusted Mean (95%CI) N	Gefitinib Adjusted Mean (95%CI) N	Adjusted mean difference at 4 weeks (95%CI) N	P-value
QLQ-C30 function scores[1]				
Physical †	-7·88 (-11·0, -0·11) 125	-5·91 (-9·17, -2·64) 113	1·97 (-2·56, 6·50) 238	0·392
Role	-11·46 (-16·30, -6·62) 123	-6·70 (-11·75, -1·64) 113	4·77 (-2·28, 11·82) 236	0·184
Emotional†	-4·33 (-7·33, -1·33) 121	-1·49 (-4·64, 1·67) 109	2·85 (-1·53, 7·22) 230	0·201
Cognitive†	-5·51 (-8·99, -2·02) 121	-3·98 (-7·65, -0·30) 109	1·53 (-3·57, 6·62) 230	0·555
Social †	-9·32 (-14·31,-4·31) 121	-0·05 (-5·32, 5·21) 109	9·26 (1·94, 16·58) 230	0·013
QLQ-C30 & OG25 symptoms scores[2]				
Fatigue	9·02 (5·32,12·71) 125	8·11 (4·23, 12·00) 113	-0·90 (-6·29, 4·49) 238	0·742
Nausea and vomiting	8·19 (4·50, 11·87) 125	8·05 (4·18, 11·93) 113	-0·14 (-5·51, 5·25) 238	0·960
Pain	6·50 (2·14, 10·87) 126	-0·31 (-4·86, 4·24) 116	-6·81 (-13·16,-0·47) 242	0·035
Dyspnoea	10·36 (5·67, 15·05) 125	4·76 (-0·17, 9·70) 113	-5·59 (-12·44, 1·25) 238	0·109
Insomnia	1·73 (-2·89, 6·34) 125	-3·38 (-8·24, 1·47) 113	-5·11 (-11·82, 1·63) 238	0·136
Appetite Loss	15·58 (9·81, 21·34) 122	12·09 (6·10, 18·08) 133	-3·48 (-11·85, 4·88) 235	0·412
Constipation	6·50 (1·31, 11·69) 125	-8·74 (-14·23, -3·26) 112	-15·24 (-22·83, -7·65) 237	0·0001
Diarrhoea	5·09 (0·01, 10·17) 121	24·3 (18·97, 29·67) 109	19·23 (11·79, 26·27) 230	<0·0001

Financial difficulties	-2·43 (-6·12, 1·27) 121	-3·76 (-7·67, 0·15) 108	-1·33 (-6·75, 4·09) 229	0·629
Reflux	2·40 (-1·22, 6·01) 120	-2·16 (-5·94, 1·62) 110	-4·56 (-9·81, 0·70) 230	0·089
Pain and discomfort in stomach	2·84 (-1·10, 6·78) 121	-1·15 (-5·29, 2·98) 110	-4·00 (-9·74, 1·75) 231	0·172
Anxiety	-3·97 (-8·11, 0·17) 121	-9·12 (-13·5, -4·78) 110	-5·15 (-11·20, 0·91) 231	0·096
Eating with others	2·05 (-2·88, 6·99) 117	0·56 (-4·60, 5·72) 107	-1·49 (-8·68, 5·69) 224	0·683
Trouble swallowing saliva	5·35 (1·22, 9·48) 121	0·78 (-3·55, 5·12) 110	-4·56 (-10·59, 1·46) 231	0·137
Choking	3·16 (-0·67, 6·98) 117	-0·02 (-3·99, 3·94) 109	-3·18 (-8·72, 2·36) 226	0·259
Dry mouth	7·40 (2·50, 12·30) 121	13·43 (8·22, 18·65) 107	6·03 (-1·17, 13·23) 228	0·100
Taste	7·33 (1·97, 12·68) 119	5·87 (0·22, 11·51) 107	-1·50 (-9·28, 6·37) 226	0·714
Cough	4·98 (0·13, 9·83) 120	-4·00 (-9·10, 1·12) 108	-8·97 (-16·06, -1·88) 228	0·013
Speech	9·46 (5·54, 13·38) 120	-0·94 (-5·05, 3·18) 109	-10·40 (-16·13, -4·67) 229	0·0004
Body image	4·92 (-0·52, 10·35) 121	5·29 (-0·46, 11·05) 108	0·37 (-7·59, 8·34) 229	0·926
Weight loss	3·43 (-1·31, 8·16) 118	4·59 (-0·36, 9·54) 108	1·17 (-5·73, 8·07) 226	0·740

[1] For global quality of life or function scores a positive adjusted mean difference implies that patients on gefitinib have less deterioration compared with those on placebo.

[2] For symptom scores a negative adjusted mean difference implies that gefitinib has less deterioration, or even improvement in symptoms, compared to those on placebo, while a positive difference implies that the symptoms have worsened more for those on gefitinib.

Figure 5: Profile plot of change in PRO from baseline to 4 weeks

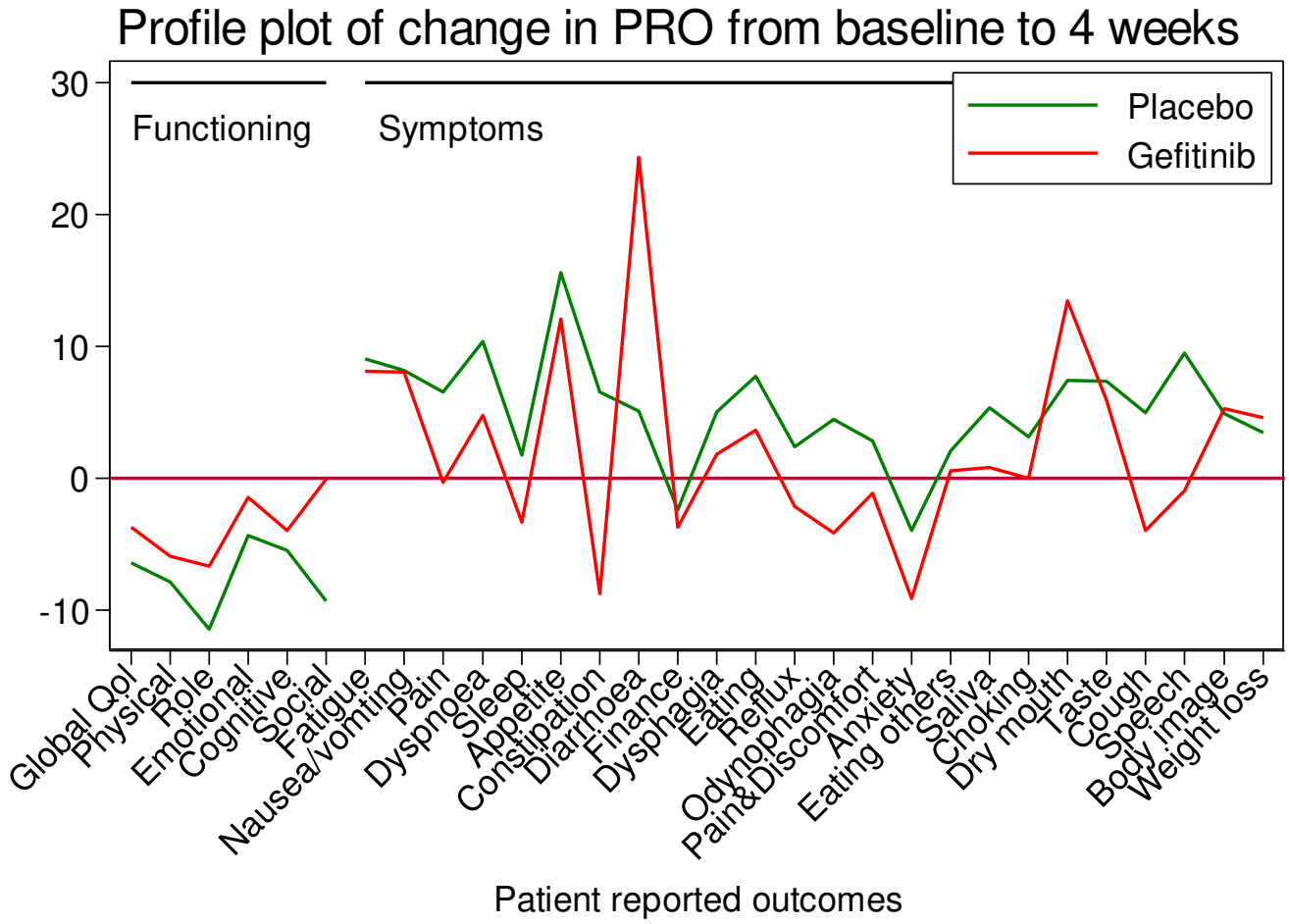


Table 1S: COG Collaborative Group Investigators

Country	City	Site	PI	Total
Scotland	Aberdeen	Aberdeen Royal Infirmary	Dr Russell Petty	**45**
England	Dudley	Russells Hall Hospital	Prof David Ferry	**42**
England	Wolverhampton	New Cross Hospital	Prof David Ferry	**40**
England	Manchester	Christie Hospital	Dr Wasat Mansoor	**37**
England	Birmingham	Birmingham Heartlands Hospital	Dr Joyce Thompson	**25**
England	Northwood	Mount Vernon Cancer Centre	Dr Mark Harrison	**24**
England	Shrewsbury	Royal Shrewsbury Hospital	Dr Anirban Chatterjee	**19**
England	Bristol	Bristol Haematology & Oncology Centre	Dr Stephen Falk	**15**
Wales	Rhyl	Glan Clwyd Hospital	Dr Angel Garcia-Alonso	**14**
England	Lancaster	Royal Lancaster Infirmary	Dr David Fyfe	**13**
England	Cheltenham	Cheltenham General Hospital	Dr Sean Elyan	**10**
England	Sheffield	Weston Park Hospital	Dr Jonathan Wadsley	**10**
England	Southampton	Southampton General Hospital	Dr Timothy Iveson	**10**
England	Guildford	Royal Surrey County Hospital	Dr Gary Middleton	**10**
England	Torquay	Torbay District General Hospital	Dr Rajaguru Srinivasan	**9**
England	Derby	Royal Derby Hospital	Dr Rengarajan Viyajan	**8**
England	Sutton	Royal Marsden Hospital (Surrey)	Dr Ian Chau	**7**
England	Salisbury	Salisbury District Hospital	Dr Timothy Iveson	**7**
England	Barrow-in-Furness	Furness General	Dr David Fyfe	**7**
Wales	Inverness	Raigmore Hospital	Dr David Whillis	**7**
England	Peterborough	Peterborough City Hospital	Dr Karen McAdam	**6**
England	Northampton	Northampton General Hospital	Dr Craig Macmillan	**6**
Wales	Aberystwyth	Bronglais General Hospital	Dr Sajid Durrani	**6**
England	Worcester	Worcestershire Royal Hospital	Dr Charles Candish	**5**
England	London	St. Mary's Hospital	Dr Danielle Power	**5**
England	Basingstoke	Basingstoke & North Hampshire Hospital	Dr Charlotte Rees	**4**
England	Dartford	Darent Valley Hospital	Dr Riyaz Shah	**4**
England	Oxford	Churchill Hospital	Dr Kinnari Patel	**4**
England	Gloucester	Gloucestershire Royal Hospital	Dr Sean Elyan	**4**
England	London	Royal Marsden Hospital (London)	Dr Ian Chau	**4**
England	Poole	Poole Hospital	Dr Virginia Laurence	**3**

England	Bournemouth	Royal Bournemouth Hospital	Dr Tom Geldart	**3**
England	Walsall	Manor Hospital	Dr Andrew Hartley	**3**
Wales	Wrexham	Wrexham Maelor Hospital	Dr Simon Gollins	**3**
England	Yeovil	Yeovil District Hospital	Dr Erica Beaumont	**3**
England	Whitehaven	West Cumberland Hospital	Dr Jonathan Nicoll	**3**
England	Coventry	University Hospitals Coventry & Warwickshire	Dr Sharmila Sothi	**3**
England	Huddersfield	Huddersfield Royal Infirmary	Dr Joanna Dent	**3**
England	Dorchester	Dorset County Hospital	Dr Mike Bayne	**3**
Wales	Bangor	Ysbyty Gwynedd	Dr Rachel Williams	**2**
Wales	Swansea	Singleton Hospital	Dr Colin Askill	**2**
England	Swindon	Great Western Hospital	Dr Claire Blesing	**2**
England	Slough	Wexham Park Hospital	Dr Marcia Hall	**2**
England	Middlesbrough	James Cook University Hospital	Dr Nicholas Wadd	**2**
England	Carlisle	Cumberland Infirmary	Dr Jonathan Nicoll	**2**
England	Wigan	Royal Albert Edward Infirmary	Dr Yeng Ang	**2**
England	Halifax	Calderdale Royal Hospital	Dr Joanna Dent	**1**
England	Hereford	Hereford County Hospital	Dr Nick Reed	**1**

Cancer Oesophagus Gefitinib

Phase III randomised, double-blind, placebo-controlled trial of gefitinib (Iressa®) versus placebo in oesophageal cancer progressing after chemotherapy

COG Trial

Oncology Clinical Trials Office, University of Oxford

Sponsored by the University of Oxford & Royal Wolverhampton Hospitals NHS Trust

EudraCT: 2007-005391-13
ISRCTN: 29580179
AZ:D7913L00059

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During office hours: Contact OCTO on telephone 01865 617016. The query will be discussed with a COG Clinical Coordinator or an appropriate member of the Trial Management Group.
Outside office hours: Call the John Radcliffe Hospital switchboard on telephone 01865 741166 and ask to call the COG Clinical Co-ordinator

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1 INTRODUCTION

1.1 BACKGROUND

GENERAL INFORMATION ON OESOPHAGEAL CANCER

Oesophageal cancer is the 5th most common cause of cancer death in the United Kingdom, with 7250 deaths occurring per annum (CRUK Cancer Stats Monograph 2004). There has been a shift in the pattern of disease in the last two decades with distal adenocarcinoma becoming the dominant site of presentation, probably in relation to increased incidence of the pre-malignant condition Barrett's oesophagus [1]. The majority of patients presenting with advanced disease are not suitable for curative intent surgery or other radical approaches. Of the approximately 25% of patients who are candidates for curative intent surgery, audits in the UK indicate that less than 25% of those operated upon live five years or more. Therefore overall cure rates are 7-8% [2] [3].

EVOLUTION OF CHEMOTHERAPY FOR ADVANCED OESOPHAGEAL CANCER

The activity of cisplatin and 5-fluorouracil (5FU) in both squamous cell and adenocarcinoma of the oesophagus was first documented in the 1980s. Although single agent activity was of the order 10-20% for both drugs [4] [5] the combination produced response rates of 20-35% in advanced disease. A randomised trial of cisplatin at 100mg/m^2 3-weekly versus cisplatin in combination with 5FU in 92 patients found a response rate of 19% versus 35% [6]. In the USA the regimen of cisplatin 80mg/m^2 plus 5FU given at 1 g/m^2 days 1-4 of a 3-4 week cycle became the standard of care, and also became widely used in stomach cancer.

In Europe, infusional 5FU first became combined in the epirubicin-cisplatin-5FU (ECF) regimen in stomach cancer [7]. In part because it is not always easy to distinguish between type II oesophageal and fundal cancers of the stomach, treatment strategies converged, but although there is less data in oesophageal cancer, there is no doubt that it is more active than cisplatin/5FU [8]. There are also clear advantages to using infusional 5FU versus short 4-5 day infusions, with less mucositis and neutropenia [7]. More recently docetaxel (Taxotere®) has been added to cisplatin/5FU (TCF) in a trial comparing TCF versus cisplatin/5FU (CF) versus ECF. There do appear to be advantages in stomach cancer and Type II oesophageal cancers, but it seems unlikely that TCF will be superior to ECF [9].

SECOND LINE CHEMOTHERAPY

Patients progressing after chemotherapy for advanced oesophageal cancer (performance status 0-2) have a median survival of around 4 months [10]. Prospective well designed phase II trials in the second line setting have only recently been reported. It is worth bearing in mind that in a phase II trial of previously treated oesophageal cancer, docetaxel at 75mg/m^2 was inactive [11]. A trial of irinotecan plus docetaxel had to be amended when docetaxel at 65mg/m^2 plus irinotecan at 160mg/m^2 3-weekly caused neutropenic fever in 4/4 patients. When the drugs were given weekly at reduced doses of irinotecan 100mg/m^2 and docetaxel 40mg/m^2 there was less neutropenia, but 9/24 patients had grade 3 or 4 non-haematological toxicity (asthenia 5, diarrhoea 3, emesis 2, constipation 1). There were 3/24 responses. Another trial used a combination of irinotecan 180mg/m^2 plus high dose infusional folinic acid at 125mg/m^2 and 5FU at 1200mg/m^2 given over 48 hours. The trial recruited largely gastric and junctional cancers. The response rate was 29%, with 26% having grade 3 or 4 neutropenia, 13.2 % having grade 3 or 4 anaemia, 13% having grade 3 or 4 vomiting. Median failure free survival was 3.7 months. In summary, second-line chemotherapeutic approaches have limited efficacy and substantial toxicity in an often poor performance status group of patients with a poor prognosis.

ROLE OF EPIDERMAL GROWTH FACTOR RECEPTORS (EGFR) IN OESOPHAGEAL CANCER

The growth factors EGF and TGFα which bind and activate the erbB1 receptor, also known as the EGFR, are known to be involved in the mitogenic process in both adenocarcinomas and squamous cell cancers of the oesophagus. EGF over-expression has been found in Barrett's oesophagus and in oesophageal cancers. In addition a high level of EGFR expression is associated with poor prognosis [12].

PHASE II CLINICAL TRIALS OF EGFR INHIBITORS IN OESOPHAGEAL CANCER

Since the first phase I trials with small molecule inhibitors of EGFR it has been possible to target the EGFR and explore the impact of these signal transduction inhibitors. The drug ZD1839, also called gefitinib (Iressa), is an orally bio available drug which has a serum half life of 46 hours [13] and at the drug levels reached at doses of 150-500mg once daily has been shown to inhibit EGFR signalling in human tissues [14].

A phase II clinical trial of gefitinib at 500mg once daily in patients with adenocarcinoma of the oesophagus has been conducted [15]. A dose of 500mg was chosen because it is well tolerated [13] and because in head and neck cancer response rates seem to be better at 500mg. Of the 27 patients treated 3 had partial response and 8 had stable disease [10]. Similar results have been obtained independently in a trial conducted in Holland [16]. Furthermore in two trials of the drug erlotinib (a similar small molecule EGFR inhibitor), responses have been seen. In adenocarcinoma patients in a SWOG trial, erlotinib at 150mg daily had 5/42 patients with partial response (Dr Andrew H. Ko, UCSF, personal communication) and in another trial 1/15 patients had response [17]. Thus in all 4 independent phase II trials of oral EGFR inhibitors, responses have been seen in both adenocarcinoma and squamous cell cancers [16].

The response rate of 10% is close to that seen in non small cell lung cancer (NSCLC) where in a randomised trial of erlotinib versus placebo in 731 patients, with disease relapsing after chemotherapy, the response rate was 8.9%, but overall median survival increased from 4.7 to 6.7 months with a hazard ratio of 0.73 ($P < 0.001$) [18]. This was the first trial of an EGFR inhibitor with a placebo arm. In the placebo arm the stable disease rate, defined as no progression after 8 weeks, was 27%, but in the erlotinib arm was 35%. Thus only 8% of patients had stable disease due to erlotinib. In the remainder, 'stable disease' was simply due to the natural history of disease in those patients. This underlines the fact that despite the partial response rate being only 9% and stable disease rate due drug being 7% (total 16%) there was a substantial effect on survival because even in the patients who progressed there was a trend to improved survival. This type of phenomenon in a clinical trial of a signal transduction inhibitor underlines the need for large randomised placebo controlled trials to accurately define the true effect of these agents.

Because of the selective targeting of the EGFR by drugs such as gefitinib, much effort has gone into defining biological characteristics of cancers which are sensitive or resistant to these drugs. Because erbB receptors activate multiple signal transduction pathways, principally through PI3-kinase–Akt –BAD (anti-apoptotic) and the ras-raf-MEK1/2-MAP-kinase (proliferation) pathways, it has been difficult to find clear correlates of response or clinical benefit. In the phase II trial a translational research component was included, where patients had oesophageal biopsies before and after gefitinib [10].

Gene expression technology was then applied, using an Affymetrix assay system which was applied to 12 paired samples. Twenty genes showed statistically significant alterations in expression following treatment with gefitinib. Interestingly, of the genes that were down regulated following treatment of gefitinib, five were oncogenes: LCN2, which is associated with HER2-positive breast cancer [19]; JAG1, which enhances angiogenesis in response to growth factors [20] LTBR , a tumour necrosis factor C receptor [21]; MNAT1, which activates and stabilises cyclin-dependent kinases [22]; and Akt1, which activates several signalling cascades such as PI-3K [23]. CASP8, an upstream protease of the apoptosis cascade, was also down regulated [24]. Although activating mutations in EGFR in a rare subtype of NSCLC termed bronchioalveloar cell lung cancer have been described [25] and to confer a high rate of sensitivity to gefitinib, these mutations are found in <1% of tumours from other sites and have not been found in oesophageal cancer in our biopsy specimens from our phase II trial (Daniel Haber, Massachusetts General Hospital MA USA).

1.2 STUDY RATIONALE

Both gefitinib at 500mg once daily and erlotinib at 150mg once daily have shown significant activity in cancers of the oesophagus previously treated with chemotherapy. We therefore propose to conduct a randomised phase III trial, with survival as the primary end point, comparing gefitinib 500mg once daily with placebo. In addition we plan to undertake a translational research project. This will run in parallel to the COG trial as a separate protocol – Histological AssessmeNt Determining EpitheliaL response (HANDEL). The technology for this project was developed during the phase II trial and is primarily based on the application of Affymetrix gene expression technology. We found that patients accepted the idea of having a biopsy both before and after commencing treatment.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

- To assess whether gefitinib will improve overall survival in patients with oesophageal cancer when compared to a placebo.

2.2 SECONDARY OBJECTIVES

- To assess the toxicity of gefitinib monotherapy in oesophageal cancer patients
- To assess whether gefitinib will have a significant positive or negative impact upon quality of life compared with placebo
- To assess the impact gefitinib will have on progression-free survival compared with placebo
- To identify if there are genetic signatures associated with benefit. (This will be done in a translational research project [HANDEL] as a separate protocol.)

3 STUDY DESIGN

3.1 TYPE OF STUDY

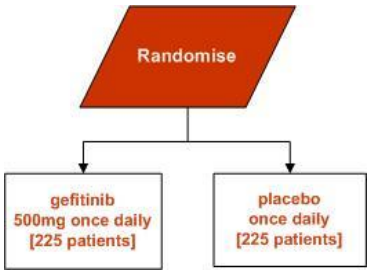
This is a national multi-centre phase III randomised double-blind placebo-controlled trial.

3.2 EXPECTED NUMBER OF PARTICIPANTS

450 (225 per arm) patients will be recruited over an 18 month period. It is anticipated that all NCRN networks will be able to participate in the treatment component of the trial.

3.3 RANDOMISATION PROCEDURE

After completing suitability checks, Consent Form for trial participation and Consent Form for blood and tissue sample collection and the Randomisation Form for the patient, site staff will call or fax a dedicated telephone number to confirm the patient's eligibility. The patient will then be randomised to one of two arms as shown below:



After randomisation has been completed, the original Randomisation Form and a copy of the patient's diagnostic pathology report (identifying the patient by trial number, initials and date of birth only), must be submitted to OCTO within 1 month.

4 ELIGIBILITY CRITERIA

Inclusion Criteria

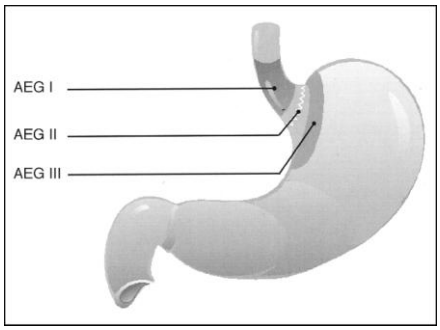
1. Age ≥ 18 years
2. Oesophageal cancers and type I and type II junctional tumours (see Figure 1)
3. Histologically proven adenocarcinoma, squamous cell cancer or poorly differentiated epithelial malignancy
4. Failure after previous chemotherapy. Treatment not to start until at least 6 weeks from the last day of chemotherapy (including oral).
5. WHO Performance Status 0, 1 or 2
6. Measurable or evaluable disease by CT scan
7. Able to take tablets (whole or dispersed)
8. Patients with brain metastases must be stable and have received cranial irradiation prior to entry

Exclusion Criteria

1. More than 2 previous chemotherapy regimens and 1 chemoradiation course.
2. Presence of previous or other malignancy likely to confound results or interfere with gefitinib therapy
3. Medical condition considered to interfere with the safe participation in the trial
4. Radiotherapy to site of measurable or evaluable disease in the last 4 weeks
5. Pregnancy
6. Sexually active patients of child-bearing potential not using adequate contraception* (male and female) [post menopausal women must have been amenorrheic for at least 12 months to be considered as having non-child-bearing potential]
7. Serum bilirubin greater than 3 times the upper limit of reference range (ULRR)
8. Aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) ≥ 2.5 x ULN if no demonstrable liver metastases (or >5 x in presence of liver metastases)
9. Any evidence of clinically active Interstitial Lung Disease (ILD) (patients with chronic, stable, radiographic changes who are asymptomatic need **not** be excluded)
10. Known severe hypersensitivity to gefitinib or any of the excipients of this product
11. On other cytotoxic chemotherapy, immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids) or experimental medications

* For female trial participants: birth control pills, approved contraceptive implant, spermicidal foam and condoms, intrauterine device, or prior tubal ligation. For male trial participants: condoms and spermicidal foams or prior vasectomy.

Figure 1: Siewert Classification (Siewert et al, 1987) for adenocarcinoma of the esophagogastric junction (AEG)



5 STUDY DRUG

5.1 NATURE AND CONTENT OF DRUG STUDY

PRE-CLINICAL EXPERIENCE

Gefitinib is an oral, specific, and potent inhibitor of EGFR associated tyrosine kinase. Key preclinical features of this compound include high tolerability and ability to delay growth and, at higher doses, cause regression in human NSCLC and a wide range of other tumour xenografts (see Investigator's Brochure for details).

ANIMAL PHARMACOKINETICS

The major route of excretion for gefitinib and its metabolites is via bile. Gefitinib is extensively metabolised to a number of components, extensively distributed outside the central compartment and rapidly cleared. Bioavailability following oral dosing is approximately 50%. Exposure to gefitinib increases approximately proportionally with dose. The plasma concentration-time profile data shows evidence of prolonged absorption occurring at the highest doses.

ANIMAL TOXICOLOGY

Gefitinib showed no genotoxic potential in-vitro. The no-effect dose level after administration of gefitinib for up to 1 month is 10mg/kg per day; at 6 months it is 1mg/kg per day. The predominant and consistent form of toxicity was epithelial and included inflammation of eyelids, folliculitis, and degeneration of hair follicles. The findings at the lowest tested dose level were similar to those in the top and intermediate dose levels when given for longer but were less severe and had a lower incidence.

Reversible ocular changes included granular/rough appearance to the cornea and corneal translucency without ulceration. Irreversible corneal opacities were seen only in the dog at the highest dose given chronically for 6 months.

Renal papillary necrosis was seen in 7 out of 20 rats given 40mg/kg/day for 1 month, and 1 out of 6 dogs given the same dose for a month.

In addition, ECG recordings revealed a PR interval increase in 2 out of 12 dogs, with large variations between the individual PR interval measurements. A second-degree atrio-ventricular block occurred in one instance; ECG findings returned to normal when therapy was discontinued.

The ophthalmologic, renal, and skin changes were considered to be related to the pharmacological activity of gefitinib. Cardiac change was considered a possible effect of gefitinib.

Biochemical or haematological abnormalities included increased white blood cells, decreased red cells, reduced plasma albumin, increased plasma liver enzymes (alkaline phosphatase [ALP], alanine transaminase [ALT], and aspartate transaminase [AST]). They were generally reversible on discontinuation of the drug. The ovaries showed a reduction in the number of corporal lutea.

CLINICAL PHARMACOKINETICS

In healthy volunteers oral gefitinib is well absorbed, with an absolute bioavailability of about 60%, and has been shown to be both extensively distributed outside the central compartment and rapidly cleared. Absorption is moderately slow with plasma concentrations typically reaching a maximum at between 3 to 7 hours after dosing. Beyond the peak, the concentrations decline in a biphasic manner, with a terminal half-life of between 10 and 83 hours. Exposure has shown up to a 20-fold range at the same dose level and was not dose proportional over the dose range 50 to 500mg with a greater than expected increase in exposure in some volunteers at the highest dose. However, the maximum degree of non-proportionality observed was only about 2 fold. On multiple dosing (utilising a double dose on day 1), exposure increased 1.3 to 2.8 fold with steady state achieved between day 3 and 5. In the fed state there was a small reduction in exposure that is not considered to be clinically significant. The major route of elimination for gefitinib and its metabolites is via the faecal route (<4% of a radiolabelled dose was excreted via the urinary route).

In cancer patients, there was up to an 11-fold range in exposure was observed within a dose group. Despite this, exposure did show an increase with dose across the dose range studied of 50 to 700mg. The terminal half-life in cancer patients ranged from 27 to 85 hours. Steady state was achieved within the first week of dosing with the variability in steady state trough concentrations within an individual patient being typically 4 to 35%.

The metabolism of gefitinib has not yet been elucidated although *in vitro* data indicated the involvement of the cytochrome P450 CYP3A4. A trial in healthy volunteers, who received a low dose, 50mg, of gefitinib alone and in combination with itraconazole (a potent CYP3A4 inhibitor), demonstrated that the mean AUC for gefitinib was increased by only 30% in the presence of itraconazole. However the combination of a single dose of 500mg gefitinib with rifampicin, a potent CYP 3A4 inducer, resulted in a 6-fold reduction in mean AUC to gefitinib which was considered to be clinically significant.

PHASE I TOLERABILITY

As of December 2000, nearly 300 cancer patients had received oral gefitinib in five separate Phase I trials. The doses tested range from 50mg to 1000mg. In each trial, expanded patient number cohorts have received escalating doses of gefitinib. In the absence of symptomatic disease progression, patients could continue to receive the same dose and schedule of gefitinib; almost 400 total patient months observation are currently available.

In three Phase I trials, dose limiting toxicity of diarrhoea has occurred; in one trial in which 64 patients received gefitinib daily for 14 days followed by no therapy for 14 days, at escalating doses, non-bloody, non mucoid, grade 3 diarrhoeal toxicity was observed at the 700mg dose level. The two largest Phase I trials, in which gefitinib is given daily without interruption, have a combined total of 142 enrolled patients, and recently completed enrolment at the highest planned dose level of 1000mg. At this 1000mg dose level, grade 3 diarrhoeal dose limiting toxicity has been reported in 4 patients. Full toxicity evaluation of this dose level is ongoing. A picture of increasing intolerability resulting in the inability to deliver planned daily therapy has emerged at doses of or greater than 600mg. At the 600mg dose level, therapy interruptions and dose reductions occurred in 3 out of 20 patients due to grade 3 skin rash (1 patient) or diarrhoeal toxicity (2 patients), in the first or second month. At the 800mg dose level, 6 out of 20 patients have been removed from the trial in the first or second month for a variety of reasons, including grade 3 diarrhoea (4 patients), transient grade 3 transaminase elevation (1 patient), and grade 4 fatigue (1 patient).

In Japan, a Phase I study in patients with solid tumours is ongoing, 4 to 6 patients per dose level (31 patients in total) have been enrolled. The grade 3 adverse reactions are elevation of AST and ALT in 2 patients (1 at 225mg, 1 at 525mg). At the 700mg dose level, grade 3 diarrhoea and transaminase elevation were dose limiting.

In these Phase I trials, consistently observed, dose-related, mechanism-based toxicity has been common and confined to the skin and gastrointestinal system; rare hepatic enzyme elevation has also occurred. Skin toxicity consists mainly of a grade 1-2 pustular rash on an erythematous base; gastrointestinal toxicity consists mainly of grade 1-2 loose or watery, intermittent, non-bloody, non-mucoid stools, occasionally with nausea or isolated episodes of emesis. Overall, the frequency of skin or diarrhoeal toxicity is greater in the continuous daily dosing schedule compared to the 14-day intermittent schedule (48% versus 35% for skin, and 44% versus 31% for diarrhoea, respectively). The majority of patients with rash at higher doses also experienced diarrhoea. Skin, gastrointestinal, and the rare hepatic toxicity rapidly reverse with drug discontinuation and/or symptomatic support.

Consistent or drug related haematopoietic, renal, and corneal toxicity have not occurred. Uveitis occurred in one patient. In 2 continuous monotherapy trials, 8.2 % of the patients experienced mild, transient adverse events related to the eye which were considered to be possibly related to trial therapy (e.g., transient redness or itchiness). Four cases of reversible corneal erosion have been reported after patients reported to their physicians that they had symptoms of pain or discomfort (accompanied by hyperaemia in 2 of the cases). Three of these cases were directly related to aberrant eyelash growth and one to a possible ocular foreign body. In 3 of the 4 patients, the condition reversed within 1 week. In the 4th patient the condition resolved within 1 week of the aberrant eyelash being detected. These adverse events happened with long-term dosing (3 to 7 months) at higher doses (400, 600, and 800mg).

All but one of the patient deaths were considered by investigators as due to disease progression. One patient's death was considered by investigators as possibly drug related however, at autopsy a large, fatal pulmonary embolus was found.

PHASE I GEFITINIB ANTI-TUMOUR EFFECT IN SOLID TUMOURS

From the Phase I trials, in 70 patients with various advanced, recurrent, previously pre-treated tumours who received gefitinib alone at doses ranging from 150mg to 800mg, clinically significant disease stabilisation was observed. In some cases of NSCLC, head and neck, and prostate cancer, objective, measurable, partial responses, or significant evaluable tumour reduction often accompanied by rapid symptom relief has been observed. Significant, confirmed radiographic antitumor response was evident in 9 patients: 3 patients (225mg, 400mg, and 700mg) had a significant regression of non-measurable, evaluable disease lasting 8.5 months and ongoing, 3.5 months and 6 months and ongoing, respectively, and 6 patients (150mg, 300mg, 400mg, 525mg, and 700mg) showed partial responses for 9 months and ongoing, 10 months and ongoing, and 7 months, respectively. Overall, more than 11% of patients in Phase I trials had stable or improved disease for at least 3 months with a median duration of 4 months (range 3 to 10 months and ongoing).

5.2 DRUG SUPPLY AND STORAGE

Gefitinib and placebo will be supplied by AstraZeneca as 250mg tablets with a matching placebo. Patients will therefore take two tablets once daily, with or without food.

Study drugs will be provided in bottles containing 200 tablets and must be stored in the original packaging with temperatures not exceeding 30°C.

COG Trial staff will supply and replenish free drug and placebo (with appropriate expiry/retest dates sufficient to complete protocol recruitment and treatment schedules) via a drug distribution agency. Any trial drugs that expire during the course of the trial will be replaced.

Upon site activation, drugs will be distributed to the participating site's pharmacy and resupplied as necessary. Bottles will be labelled with a unique number, which will facilitate the allocation of gefitinib/placebo without the blind being broken. Following randomisation, sites will be informed of which bottles to dispense to each patient.

COG Trial staff will monitor supplies at each site. However if a site is concerned about stock levels, the local pharmacist should contact COG trial staff to discuss the matter further.

5.3 ACCOUNTABILITY

Participating pharmacies will maintain all fields of the COG Dispensing Log for each patient. This Log must be available for inspection by COG Trial staff, AstraZeneca and worldwide regulatory government agencies as required. Upon completion of Protocol treatment, each original Dispensing Log must be returned to OCTO with a copy retained on site. Data entered onto the log will be entered onto the COG database and queries raised as necessary.

Patients should return any overage from a previous supply when collecting new supplies of trial medication, approximately every 3 months. Where possible, patients should be contacted prior to these visits to remind them to bring their tablets back in with them, or the empty bottle if applicable. Patients who discontinue trial medication but continue to be followed up must also be encouraged to return any remaining supplies.

All unused tablets must be logged on the Dispensing Log and destroyed in accordance with local procedures. In such circumstances, completion of a Drug Destruction Form is **not** required.

If drug supplies are destroyed on site in error or if a batch has expired, a Drug Destruction Form must be completed and sent to OCTO. Drug Destruction Forms are available in each site's pharmacy file or from COG Trial staff upon request.

Drug Enquiries

Sites must contact the COG trial office on +44(0)1865 617016.

5.4 CONCOMITANT MEDICATION

No other cytotoxic chemotherapy, immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids) or experimental medications will be permitted while patients are on trial medication. Disease progression requiring other forms of specific anti-tumour therapy will be a cause for early discontinuation of protocol treatment.

All concomitant medications will be recorded in the patients' hospital notes. These will not be recorded in the CRFs unless an interaction is suspected by the investigator.

6 STUDY TREATMENT

Patients will be randomised to receive either gefitinib 500mg once daily or placebo. The primary end point will be survival. Quality of life will be assessed and a biopsy study (HANDEL) using DNA-microarray technology will be used to identify genes associated with response and prognosis. Gefitinib is a licensed drug for NSCLC (non-small-cell lung cancer) however is being used in this study for oesophageal cancer.

6.1 ARM A

Gefitinib 500mg once daily (2 x 250mg tablets).

6.2 ARM B

Placebo once daily (2 x 250mg tablets).

6.3 DOSE MODIFICATIONS

The most likely toxicities with gefitinib at 500mg once daily are diarrhoea and acniform skin rash. Dose reductions may only be made once (i.e. from two tablets/day to one tablet/day). No further dose reductions are permitted.

NON-HAEMATOPOIETIC TOXICITY

In the event of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4 non-haematopoietic Adverse Events (AEs) that the investigator considers due to suspected disease progression, re-evaluation of tumour status is indicated irrespective of scheduled clinic visits.

In the following circumstances, administration of gefitinib/placebo may be interrupted for a maximum of 14 days to allow the AE to resolve or decrease in severity [NB multiple treatment breaks of ≤14 days per break are permitted]:

- CTCAE grade 3 or 4 or unacceptable toxicity, e.g., cosmetic effect of grade 2 rash
- There is no consideration and/or corroborative evidence that the AE is due to progressive disease
- AE is consistent with toxicity described in the Investigator Brochure

At a minimum, re-assessment of toxicity should be done twice weekly and more frequently if clinically indicated. Once the AE decreases in severity to CTCAE grade 1, the patient may continue to take the assigned dose. If the AE resolves to grade 2, the investigator may elect to decrease the patient's dose to one tablet once daily.

If a dose or doses are missed, the reason(s) and the number of doses not taken should be noted and recorded on the appropriate CRF. Every attempt should be made to manage possible drug-related toxicity so that a patient remains evaluable for efficacy.

SKIN TOXICITY

In the event of CTCAE grade 3 or 4 pustular rash, secondarily infected rash, or a rash/skin condition intolerable to the patient due to pruritis, aesthetics, etc., gefitinib/placebo may be discontinued for a maximum of 14 days until the rash resolves, improves to grade 1, or is within patient tolerability. Gefitinib/placebo may then be resumed. It is recommended that patients be given a drug interruption prior to a dose reduction. Unless, in the investigator's opinion, the toxicity is unlikely to be resolved by the drug interruption. Dose reduction applies only to those patients

taking two tablets per day. Of note, many patients were able to resume gefitinib/placebo therapy at the same dose after resolution of rash and had less extensive and/or severe rashes.

NAUSEA AND/OR VOMITING

In patients who have emesis and are unable to retain gefitinib/placebo for 30 minutes or longer, every attempt should be made to obtain control of nausea and vomiting. The dose of gefitinib/placebo may be repeated if emesis occurs within 30 minutes of taking the tablet(s).

DIARRHOEA

In the event of grade 1 diarrhoea, no specific supportive care is usually needed or indicated beyond the use of anti-diarrhoeals.

In the event of diarrhoea CTCAE grade 2-4 occurring, immediate appropriate supportive care measures should begin. Gefitinib/placebo should be discontinued up to a maximum of 14 days until the diarrhoea resolves completely or becomes grade 1 when treatment can be restarted.

If diarrhoea recurs and if the investigator feels the diarrhoea is clearly treatment related and no other etiology is identified, patients may receive a dose reduction to one tablet once daily.

If, despite the dose reduction, grade 2-4 diarrhoea recurs, gefitinib/placebo must be discontinued and appropriate supportive care measures should be given as above. The patient withdrawn from trial medication and the appropriate CRFs completed and submitted to COG Trial staff.

MISSED DOSES OF TRIAL THERAPY FOR REASONS OTHER THAN TOXICITY

If a dose is missed on a particular day, the date(s), and the reason the dose was not taken should be noted and recorded on the appropriate CRF. Trial treatment should be resumed the next day. Patients must **not** take a double dose the following day.

DURATION OF TRIAL THERAPY AND POST-TRIAL TREATMENT

Duration of trial therapy will depend upon when a patient is recruited into the trial. Recruitment will last for 18 months and the trial will close six months after the last patient is recruited or when 389 deaths have occurred, which ever is later. Upon trial closure, any patients continuing to show evidence of response, disease stabilisation, or clinical benefit from trial therapy and was randomised to Arm A may be able to continue on gefitinib therapy if the treatment is still being supplied. In such circumstances, sites should contact COG Trial staff for more information. See RECIST Criteria in the Appendices for more information.

6.4 WITHDRAWAL AND ADDITIONAL TREATMENT

TERMINATION OF TREATMENT

Below are the criteria for early termination of protocol treatment:

- Intolerable side effects as judged by the investigator or patient
- Treatment is suspended for >14 days due to toxicity
- Patient decision to discontinue treatment
- Pregnancy (complete Pregnancy Notification Form)
- Grade 3 or 4 non-haematological toxicity on the reduced dose of one tablet daily
- Tumour progression or stable disease with obvious symptomatic deterioration (e.g. patients with bone metastases who cannot walk)
- Serious systemic allergic response to trial therapy, e.g. angio-oedema, anaphylaxis or bronchoconstriction
- Any other reason if deemed medically necessary by the investigator

At treatment withdrawal, a full assessment must be performed consisting of a clinical examination (including vital signs, weight, and WHO Performance Status), FBC and biochemistry profile, quality of life and adverse event monitoring ($\geq$Grade 2, until resolution of all toxicities).

If not already carried out, patients withdrawing prematurely from trial treatment due to progressive disease or other reasons should whenever possible have disease measured by CT scanning.

Despite early termination of protocol treatment, all patients will continue to be followed-up for survival.

ADDITIONAL TREATMENT

Those patients who have terminated protocol treatment can receive additional treatment with full supportive care. No patients should receive a therapy targeting EGFR, including erlotinib, cetuximab or other experimental agents which target EGFR during participation in the trial.

RADIOTHERAPY

Palliative setting - there should be an interval of 2 days between the last dose of trial drug and the start of palliative radiotherapy.

6.5 OVERDOSE

There is no specific treatment in the event of overdose of gefitinib, and possible symptoms of overdose are not established. However, in phase I clinical trials, a limited number of patients were treated with daily doses of up to 1000mg. An increase of frequency and severity of some adverse reactions was observed, mainly diarrhoea and skin rash. Adverse reactions associated with overdose should be treated symptomatically; in particular severe diarrhoea should be managed appropriately.

6.6 SPECIAL PRECAUTIONS

LIVER TRANSAMINASES

Gefitinib should be used cautiously in the presence of mild to moderate increases of liver transaminases. Discontinuation of trial medication should be considered if changes are severe.

PATIENTS ON WARFARIN

International Normalised Ratio (INR) elevations and/or bleeding events have been reported in some gefitinib treated patients taking warfarin. Patients taking warfarin should be monitored regularly for changes in Prothrombin Time or INR.

INTERSTITIAL LUNG DISEASE

Interstitial lung disease (ILD), including interstitial pneumonitis, is a common complication of lung diseases including advanced lung cancer, regardless of treatment. It has also been widely observed in clinical trials in which chemotherapy (incidence generally ranges from 3-6%) and/or radiotherapy (incidence generally ranges from 10-15%) has been used for the treatment of advanced lung cancer.

Interstitial Lung Disease, which may be acute in onset, has been observed uncommonly in patients treated with gefitinib. These patients usually present with a fairly acute onset of dyspnoea sometimes associated with cough or low-grade fever. This may become quite severe within a short period of time and usually results in hospitalisation. Radiological investigations, often including computerised tomography (CT) scan, frequently show pulmonary infiltrates or interstitial shadowing with ground glass appearance. There is often respiratory distress with arterial oxygen desaturation. Cultures are frequently negative for bacterial growth. In a number of cases, the event has responded to steroid therapy but this is not always so and some cases have been fatal. Patients with concurrent idiopathic pulmonary fibrosis, interstitial pneumonia, pneumoconiosis, radiation pneumonia or drug-induced pneumonia, have been observed to have an increased mortality rate from this condition

If patients present with an acute worsening or new onset of respiratory symptoms such as dyspnoea, cough and fever, trial medication should be interrupted and the subject promptly investigated for ILD. If ILD is confirmed, trial should be discontinued and the subject treated appropriately.

RENAL

Asymptomatic laboratory elevations in blood creatinine have been observed. No significant deterioration in the renal function of those patients who entered the monotherapy studies with mild-to-moderate renal impairment has been observed. There are insufficient data, due to the small numbers of patients with severe renal dysfunction, to evaluate the safety profile of gefitinib in patients with severe renal impairment. It is recommended that periodic renal function tests are performed.

CONCOMITANT MEDICATION

Although no PK/PD relationship has been established for gefitinib, it is reasonable to believe that co-medication with rifampicin and with other CYP3A4 inducers (e.g. phenytoin, carbamazepine, barbiturates or St John's Wort) may potentially reduce efficacy.

7 STUDY EXAMINATIONS AND ASSESSMENTS

7.1 CLINICAL ASSESSMENTS

Assessments will be conducted as defined in the chart as follows. All clinical assessments are in accordance with standard clinical practice. Visit 1 = date of first dose of trial medication and can be the same date as Baseline visit.

	Baseline Visit[a]	Visit 1 [treatment start date]	Visit 2/ 4 weeks post V1*	Visit 3/ 8 weeks post V1*	Visit 4/ 12 weeks post V1*	Visit 5/ 16 weeks post V1*	Follow up every 8 weeks [24, 32, etc. weeks post V1*]
History	x						
Physical examination	x		x	x	x	x	X
Performance status	x		x	x	x	x	X
Weight	x		x	x	x	x	X
Body Surface Area	x						
Vital signs	x		x	x	x	x	X
Full Blood count	x		x	x	x		
Biochemistry[b]	x		x	x	x		
Creatinine Clearance[c]	x						
Concomitant medication	x	x	x	x	x	x	X
CT Scan (thoracic & abdomen)	x		x	x		x	x
Quality of Life Assessment[d]	x		x	x	x		
Toxicity			x	x	x	x	x
Study treatment dispensed[e]		x			x		As required

a Baseline: All to be carried out after consent, prior to randomisation and within **TWO** weeks prior to the start of treatment, except thoracic/abdominal CT scan which can be done up to **FOUR** weeks prior to the start of treatment.

b Biochemistry to include: Urea, Cr, Na, K, Ca, Alb, Bilirubin, Alk.phos, ALT and AST (note ALT and AST at Baseline, V1 and V2 only).

c Cockcroft-Gault Formula (see Appendices).

d Quality of Life assessments to be completed by patients at Baseline Visit prior to commencing treatment and within 7 days of Visits 2, 3 and 4. Patients are not required to complete assessments following confirmation of disease progression.

e Approximately every 3 months.

* V1 Visit 1.

After four weeks of gefitinib or placebo patients will have a CT scan to define response according to RECIST criteria (see Appendices) and the following action will be taken:

- Patients with progressive disease will discontinue randomised treatment
- Patients with response will be allowed to continue randomised treatment if they wish
- Patients with stable disease and with obvious symptom deterioration should discontinue randomised treatment
- Those with stable disease and with symptom improvement or stabilisation may be offered the opportunity of continuing randomised treatment. This is at the discretion of the local investigator.

7.2 QUALITY OF LIFE ASSESSMENTS

The primary outcome of this trial is survival but Health-Related Quality of Life (HRQL) is an important secondary outcome. Accurate assessment of HRQL may critically inform the trial recommendations. The main objective of HRQL assessment within this clinical trial therefore is to compare the differences in HRQL between patients randomised to gefitinib 500mg once daily with HRQL in patients receiving the placebo.

The HRQL issues that will be measured will include generic and disease specific aspects of HRQL relevant to oesophageal cancer and treatment specific issues associated with gefitinib. It is hypothesised that patients in the intervention arm will report better HRQL (improved global HRQL, relief of dysphagia, fewer eating restrictions, reduction in pain) than the placebo group because of better disease control, in spite of possible increased problems due to treatment-related toxicity (increased problems with diarrhoea, nausea and vomiting and fatigue).

HRQL will be assessed using the EORTC Quality of Life Questionnaire (QLQ-C30) version 3.0 [26]. This is an extensively validated generic cancer instrument composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social and cognitive), three symptom (fatigue, nausea and vomiting and pain), global health status/overall 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 HRQL in patients with oesophageal cancer and these will be assessed using the disease specific module, EORTC QLQ-OG25. This has been developed and validated in patients undergoing treatments for cancer of the oesophagus, oesophago-gastric junction and the stomach [27]. It includes scales assessing eating restrictions, dysphagia, reflux and pain.

Patients are eligible for the HRQL assessment in this study if they fulfil the eligibility criteria and complete the baseline HRQL questionnaires before treatment commences. Patients will be informed in the patient information sheet that they will have their HRQL assessed regularly while involved in this trial.

Patients will be asked to complete HRQL questionnaires after consenting to participate in the trial, prior to randomisation and within 14 days before the start of treatment. 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 Follow up questionnaires will also be completed at 4, 8 and 12 weeks after commencement of treatment. This will total a maximum of four HRQL assessments per patient (patients who have progressed will not be asked to complete the assessments). The time windows for eligible follow up will be +/- seven days of the expected assessment time. All questionnaires will be completed during the scheduled hospital visit and reasons for non-completion will be recorded.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual [28]. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where: 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/HRQL represents high HRQL.

The sample size calculation for the main study has been performed based on the primary outcome measure, survival. HRQL is an important aspect of this trial and all patients will be encouraged to complete questionnaires at each time point unless disease progression has occurred. For each of the main HRQL endpoints a clinically important difference of 10 points in the mean score between the treatment arms would be detectable at the 5% significance level with 80% power if data is available on 380 patients at 4 weeks. HRQL is an important trial endpoint and therefore all sites are required to participate in this aspect of the trial. A named person, recorded on the Site Contact & Responsibilities Sheet, at each participating site must be nominated to take responsibility for the administration, collection and checking of quality of life questionnaires. An information pack will be sent to all participating sites detailing the procedures for HRQL assessment and providing guidelines for ensuring optimal compliance.

Questionnaires will be collected when the patient attends the hospital. The timing of assessments will be coordinated with routine clinic visits. For all patients, quality of life will be assessed on a maximum of four occasions (pre-treatment and 4, 8 and 12 weeks post-treatment, or until disease progression, whichever is sooner).

8 PATIENT SAFETY

8.1 ADVERSE EVENT DEFINITIONS

ADVERSE EVENT (AE)

An adverse event is defined as any untoward medical occurrence in a patient to whom a drug has been administered; the event does not need to have a causal relationship to the trial drug(s), but symptoms of the targeted cancer should not be classed as an adverse event.

ADVERSE REACTION (AR) OR ADVERSE DRUG REACTION (ADR)

An adverse reaction or adverse drug reaction is any untoward and unintended responses to an investigational medicinal product related to any dose administered.

SERIOUS ADVERSE EVENT (SAE) OR SERIOUS ADVERSE DRUG REACTION (Serious ADR)

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in offspring of patient regardless of time to diagnosis)
- Other important medical event(s)***

* The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

*** Other events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above (excluding new cancers or result of overdose).

UNEXPECTED EVENT

This is an event that is not listed as a known toxicity of the trial drug in the Investigator Brochure (IB).

SUSAR

A SUSAR is a Suspected Unexpected Serious Adverse Reaction. All SUSARs will be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) and main Research Ethics Committee in accordance with the local adoption of the EU Directive 2001/20/EC and 2005/28/EC.

INVESTIGATOR ASSESSMENT

SERIOUSNESS

When an AE/AR occurs the investigator responsible for the care of the patient must first assess whether the event is serious using the definition in section 8.1.

EXPECTEDNESS

An expected event is defined as an event listed in the Investigator Brochure at the same severity/frequency.

CAUSALITY

The Investigator must assess the causality of all serious events/reactions in relation to the trial therapy using the definitions below. There are five categories: unrelated, unlikely, possible, probable and definitely related.

Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

8.2 SERIOUS ADVERSE EVENT (SAE) REPORTING

All SAEs (except for deaths and hospitalisation which are disease related*) must be reported, irrespective of causality or expectedness, in accordance with the following procedure:

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

- COMPLETE a Serious Adverse Event Form
- In the absence of the responsible Investigator (as named on the Site Contact & Responsibilities Sheet), the form must be completed and signed by a member of the site trial team and faxed to COG Trial staff immediately. The form must then be checked, any changes made, signed and re-faxed by the Investigator as soon as possible.
- SEND (by fax, within 24 hours of becoming aware of the event) the signed and dated Serious Adverse Event Form to COG Trial staff. **Fax: 0800 3891629**

  NB the form must still be faxed within this time period, even if an Investigator's signature is not yet available.
- NOTIFY Local Ethics Committee, or other local body (e.g. R&D Department) of the event, if required, in accordance with local practice

*Deaths which are disease related are end points and therefore do not require reporting as SAEs. Likewise hospitalisation solely due to confirmed disease progression, do not require reporting as SAEs but the relevant CRF should be completed. Other hospitalisation as defined in Section 8.1 should still be reported as an SAE.

COG Trial staff will report all SUSARs to the main REC, within required timelines. All SUSAR reports submitted to the MHRA have to be unblinded. Therefore, COG Trial staff will obtain the unblinded treatment information from the Centre for Statistics in Medicine (as detailed in section 8.4) and forward all SUSAR reports to the MHRA within the required timelines. AstraZeneca will also be informed of the event as per Appendix 14. All reportable events serious and unexpected and drug related/unknown relationship, and any others as advised by the main REC, will be sent to Investigators for submission to their local ethics committees or other body, if required, in accordance with local practice.

COG Trial staff will send a safety report to the main REC, MHRA and CTRG (Clinical Trials and Research Governance) at the University of Oxford (sponsor) annually. Sites should forward this report to their local R&D department if required in accordance with local practice.

In the case of a Serious Adverse Event, the patient must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the patient's status is unlikely to change further. Follow-up may continue after completion of protocol treatment if necessary. COG Trial staff will liaise with the site to resolve queries as necessary.

Follow-up information will be noted on the 'Serious Adverse Event Form' by ticking the box marked 'follow-up' and send to COG Trial staff as information becomes available. Extra annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number, date of birth and initials only. The patient's name must **NOT** be used on any correspondence.

If the event leads to the patient's withdrawal from trial medication, the relevant CRFs must also be completed and submitted to COG Trial staff.

All new events must be reported up to 30 days after the last date trial medication was taken. If an unreported event from this time period is identified at a later date, retrospective reporting must occur immediately. Events occurring outside of this time period may still be reported if the local Investigator feels that it is medically important.

In the case of death, wherever possible, a copy of the death certificate should be submitted to COG Trial staff.

In the case of death or life-threatening events telephone (on day of awareness) COG Trial staff. **Telephone: 01865 617016.**

All SAEs will be subjected to a clinical review by a panel inclusive of the Chief Investigator (CI) and a clinical coordinator from OCTO to determine whether sufficient information has been provided and whether any further information should be requested. In the instance where the SAEs occur at any of the clinical reviewer's site, these SAEs will be reviewed by the other clinical coordinators. Adverse event data will also be reviewed 6 monthly by the COG Data and Safety Monitoring Committee (DSMC).

8.3 ADVERSE REACTION (AR) OR ADVERSE DRUG REACTION (ADR) REPORTING

All Adverse Reactions/toxicities must be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE). Full listings of the current version of the CTCAE can be obtained from COG Trial staff or from: http://ctep.cancer.gov/reporting/ctc.html.

Please note for ARs/toxicities diarrhoea and skin rash a CTCAE of 2, 3 or 4 needs to be recorded on the relevant Adverse Reaction/Toxicity Form. For all other AR/toxicities only a CTCAE of 3 or 4 needs to be recorded. All ARs/toxicities are to be recorded up to 30 days post the end of treatment. All original Adverse Reaction/Toxicity Forms must be sent to OCTO for all patients 30 days after the end of treatment and faxed on request.

Any toxicity incurred but not categorised by the CTCAE should be graded by the physician and be recorded using a scale of mild (1), moderate (2), or severe (3) on the relevant CRF. Please refer to Appendix 4 for a list of side effects associated with gefitinib.

8.4 CODE BREAKING – UNBLINDING OF RANDOMISED TREATMENTS

The treatment code will be broken at trial closure for all patients. In the rare event that a patient requires emergency code break, site staff are to do the following. During office hours (Monday to Friday, 9:00-17:00 - GMT/BST), site staff will fax a Code Break Notification Form to the COG trial office on 0800 389 1629. The request will be reviewed by a COG Clinical Coordinator. If approved, COG trial staff will contact the Centre for Statistics in Medicine (CSM), where the code break information is securely held. CSM will notify OCTO of the treatment arm and OCTO will pass the information on to the site by fax. Outside office hours, site staff will contact OCTO by fax and the request will be dealt with on the next working day. If the code break request is not approved, sites will be notified accordingly.

While waiting for a decision from the clinical review, treating clinicians should withhold the investigational drug and treat the medical problem in the most appropriate manner with all the supportive care required. It should always be assumed that the drug the patient is on the active arm of the trial (i.e. taking gefitinib). Gefitinib is considered to be a cancer agent of low toxicity and 24-hour clinical query telephone cover (as detailed on Page 2 of this protocol) will be provided for by the COG Trial Office.

Patients who have had the treatment code broken and are found to be on the active arm (gefitinib), may continue to stay on the treatment if it is shown that they are benefiting from it. These patients will no longer be required to complete the HRQL forms as from this point onwards, but will continue to be followed up for progression and survival. Code breaking should be avoided wherever possible.

Any unblinding of treatments during the trial will be listed and summarised separately by treatment group (numbers, percentages).

8.5 PREGNANCY

If a female trial patient becomes pregnant or the partner of a male trial patient conceives whilst on trial, or within 3 months following the last dose of trial medication, OCTO must be notified immediately using the Pregnancy Notification Form. Female patients must stop taking the trial medication immediately. Upon completion of the pregnancy OCTO will need to be notified of the outcome using an additional Pregnancy Notification Form.

9 STATISTICAL CONSIDERATIONS

9.1 CALCULATION OF SAMPLE SIZE

Patients will be randomised to the two treatment groups using variable permuted block randomisation but no stratification.

Previous Phase II trials [29] [30, 31] in second line treatment for oesophageal cancer have reported a 10% 1-year survival. An improvement in 1-year survival in the gefitinib group to 18% would be clinically important. For this difference to be significant at the 5% (p=0.05) two-sided level with 82.5% power, allowing for a 10% loss to follow-up, 18 month recruitment and at least 6 month follow-up of all patients, 450 patients are required (225 in each treatment arm). This calculation was carried out using the artsurv procedure in STATA 9.

This calculation includes a 10% loss to follow-up, which is erring on the side of caution since the median survival is short. The non-compliance rate is expected to be low and this has not been allowed for on top of the 10% loss to follow-up.

9.2 STUDY OUTCOME MEASURES

PRIMARY OUTCOME MEASURE

- **Overall survival** where length of survival is defined in whole days, as the time from randomisation into the trial to death from any cause; for those patients who are not observed to die during the course of the trial, the length of survival will be censored at the last known follow-up date. Follow-up occurs at 4, 8, 12 and 16 weeks after start of treatment and then every eight weeks until the end of the trial.

SECONDARY OUTCOME MEASURES

- **Toxicity and Safety** will be measured by comparing the toxicity profiles for the two treatment arms.
- **Quality of life** will be assessed using functions, scales and items from the HRQL instruments EORTC QLQ-C30 and EORTC QLQ-OG25 (see Section 7.2 and Appendices). The main focus of the quality of life comparisons will be: Global health status/QoL; Dysphagia; Eating and Pain. Other HRQL variables will be examined exploratively.
- **Progression free survival**, defined as the time from randomisation until clinical or radiological (as defined by the RECIST criteria - see Appendices) progression or death from any cause. CT scans are carried out at baseline, then at 4, 8 and 16 weeks post treatment start date and then every eight weeks.
- **Identification of a genetic signature** – this will be investigated in a separate sub study (HANDEL).

9.3 STUDY ANALYSIS

All patients who are randomised into the trial will be analysed on an intention-to-treat basis. The survival for the two treatment arms will be compared in one analysis using Kaplan-Meier survival curves and a log-rank test. Cox (proportional hazards) regression will also be carried out to allow for any prognostic factors for oesophageal cancer and for factors with an imbalance in the treatment groups.
Toxicity data will be reported descriptively.

Progression free survival for the two treatment arms will be compared in one analysis using Kaplan-Meier survival curves and a log-rank test. Cox (proportional hazards) regression will also be carried out to allow for any prognostic factors for oesophageal cancer and for factors with an imbalance in the treatment groups.

Quality of life: the main comparison of the quality of life endpoints will be to compare the two treatment arms at 4 weeks, adjusting for baseline values using ANCOVA. Further investigation into quality of life functions and scales will be reported using longitudinal statistical methods and imputation of missing data will be carried out where appropriate. Imputation of missing values will not be implemented where there are missing forms due to attrition because of disease progression.

SUBGROUP ANALYSES

No subgroup analyses are planned. However based upon the data from the genomic study it may be possible to identify subgroups of patients with molecular signatures associated with benefit.

INTERIM ANALYSIS

The primary and secondary aims will only be considered at the end of the trial, with the exception of the safety and toxicity data which will be provided to an Independent Data and Safety Monitoring Committee (DSMC) every 6 months during recruitment. Analyses for the other aims will only be provided if specifically requested by the DSMC.

FINAL ANALYSIS

The trial is expected to complete recruitment within 18 months. Final analysis will begin after all patients have been followed up for at least 6 months and after 389 deaths have been recorded.

9.4 MILESTONES

It is anticipated that approximately 50 sites will be involved in the study. The trial aims to complete recruitment of 450 patients within 18 months. A recruitment rate of 20-30 patients per month is expected.

September 2008	Open trial to recruitment
March 2009	First DSMC for safety and recruitment assessment (150 patients randomised)
September 2009	Second DSMC (300 patients randomised)
September 2011	End of recruitment (450 patients recruited)
April 2012	Start of final analysis

10 STUDY ORGANISATION

This is a phase III, multi-centre trial Co-Sponsored by the University of Oxford and the Royal Wolverhampton Hospitals NHS Trust. The sponsor's UK contact point is Heather House, and the address is Clinical Trials and Research Governance (CTRG), University of Oxford. The COG Trial will be co-ordinated by the Oncology Clinical Trials Office (OCTO).

COG is an independent, investigator-led trial conducted with a study grant from CRUK and free drug supplies from AstraZeneca.

10.1 STUDY RESPONSIBILITIES

The Principal Investigator (the lead clinician for the study site) has overall responsibility for the study and all patients entered into the study, but may delegate responsibility to other members of the site team as appropriate e.g. drug supplies managed by the on-site pharmacist, trial forms completed by the Data Manager. The Principal Investigator must ensure that all staff involved in the study are adequately trained and their duties have been logged on the Site Contact & Responsibilities Sheet. COG Trial staff must be provided with updated information when staff or responsibilities change.

For further information on trial responsibilities, please refer to the ICH GCP guideline (E6). Copies can be obtained from COG Trial staff or printed from www.ich.org

10.2 STUDY START-UP

Sites wishing to take part in the study should contact COG Trial staff to obtain trial information and start-up packs (containing relevant core documents, ethics submission information/documents and regulatory submission information/documents). A Principal Investigator must provide COG Trial staff with all core documentation and attend an investigator meeting/call before the site becomes activated (usually carried out as a telephone conference). A training phone call will also be completed with the site's main contact (usually a research nurse and pharmacist).

COG Trial staff will also call to check that the site has all the required study information/documentation and is ready to recruit. The site will then be notified by e-mail once they are activated on the COG database and able to randomise. This information will be sent to the site's PI, main contact and pharmacist, and drug supplies will be dispatched.

10.3 CORE DOCUMENTS

These documents consist of:

- Clinical Trial Agreement
- Site Contact & Responsibilities Sheet
- Confirmation of a favourable Site Specific Assessment (SSA)
- Trust R&D approval letter

All Investigators and Co-Investigators must provide their current CV, personally signed and dated, prior to participating in the study. The CV should detail the Investigator's education, training and experience relevant to their role in this trial. A CV template is available on request from COG Trial staff. CVs already held at OCTO for other trials may be used for participation in COG. An updated CV will be requested approximately every three years. All CVs will be held securely with restricted access.

If circumstances change at the site (e.g. change of Principal Investigator, hospital address etc.) new documents must be completed and sent with a cover letter to COG Trial staff.

11 STUDY PROCEDURES

11.1 RANDOMISATION PROCEDURE

The randomisation system will ensure that there is no bias between the two treatment groups. Randomisations take place after patient consent has been gained and within **TWO** weeks of all baseline assessments except thoracic/abdominal CT which can be done within **FOUR** weeks prior. A Randomisation Form must be completed prior to randomisation. These details can be phoned or faxed to OCTO:

Telephone: 0800 3891635
Fax: 0800 3891629

After checking eligibility and recording baseline patient details, treatment will be allocated by computer from pre-generated lists of block randomised treatment allocations. These lists will only be accessible to staff within OCTO. The patient trial number and trial medication bottle numbers will be given over the telephone and confirmed by fax.

After patients have been randomised, the investigator must send the patient's General Practitioner a letter and copy of the Patient Information Sheet to inform them that their patient is participating in the trial (see Appendices).

The original Randomisation Form must be submitted by post to OCTO, with a copy of the diagnostic pathology report and the completed Consent Notification Form.

A Screening Log must be maintained to document all patients considered for the trial but subsequently excluded. Where possible, the reason for non-entry to the trial must be documented. This must be faxed to COG Trial staff monthly and as requested.

11.2 CASE REPORT FORM (CRF) COMPLETION

Each site will be provided with an Investigator File containing relevant trial information and CRFs. Data collected on each patient will be recorded by the Principal Investigator, or his designee (as noted on the Site Contact & Responsibilities Sheet), as accurately and completely as possible. The Principal Investigator will be responsible for the timing, completeness, legibility and accuracy of the CRF and he/she will retain a copy of each completed form. The Principal Investigator will allow study staff access to any required background data from such records (source data e.g. medical records) on request.

Following randomisation, sites will be provided with a patient-specific CRF schedule detailing the required CRFs and dates on which each is due to be completed and sent to COG Trial staff.

Entries must be made in black ballpoint pen on the CRF provided and must be legible. Errors must be crossed out with a single stroke, the correction inserted and the change initialled and dated by the Investigator. If it is not clear why the change has been made, an explanation must be written next to the change. Correction fluid must not be used. Each patient must have the correct CRFs completed and signed by the Principal Investigator (or designee). This applies to those patients who fail to complete study treatment. All data submitted on CRFs must be verifiable in the source documentation or the discrepancies must be explained.

CRF pages should be sent to:

FREEPOST RRTL-ALZY-CBRL, Oncology Clinical Trials Office (OCTO), COG Trial, Department of Clinical Pharmacology, University of Oxford, Old Road Campus Research Building, Old Road Campus off Roosevelt Drive, Headington, Oxford, OX3 7DQ.

11.3 PROTOCOL COMPLIANCE AND MONITORING

COG is being conducted under the auspices of the Cancer Research UK according to the current guidelines for Good Clinical Practice.

The trial staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and any queries that they may have. COG Trial staff will check incoming forms for compliance with the protocol, consistent data, missing data and timing. Investigators will allow the study staff access to source documents as requested. Sites may be withdrawn from further recruitment in the event of serious and persistent non-compliance.

12 ETHICAL AND REGULATORY STANDARDS

12.1 ETHICAL PRINCIPLES

The trial will be coordinated by COG Trial staff at OCTO, The University of Oxford in the UK. The office will conduct the trial according to its local adoption of the ICH GCP Guidelines and OCTO SOPs. Copies of the ICH GCP guidelines can be obtained from COG Trial staff or via the internet: www.ich.org

Patients have the right to withdraw from the trial at any time for any reason.

This trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989), South Africa (1996) and Scotland (2000) amendments. Copies can be obtained from COG Trial staff or via the internet: http://www.wma.net

COG will be conducted in accordance with the EU Directive 2001/20/EC and 2005/28/EC.

12.2 INFORMED CONSENT

It is the responsibility of the Principal Investigator (or designee as listed on the Site Contact & Responsibilities Sheet and locally approved) to obtain written informed consent in compliance with national requirements from each patient prior to entering the trial or, where relevant, prior to evaluating the patient's suitability for the trial. The trial should be discussed in detail with the patient, by one of the research team appropriately listed on the Site Contact & Responsibilities Sheet (e.g. clinician or nurse) and the patient provided with a copy of the Patient Information Sheet to take away with them to consider further. Patients should be given sufficient time (e.g. one week) to consider the trial, allowing time for discussion with family/friends and their GP, and for the patient to ask questions of the research team prior to written consent being given.

Copies of the Patient Information Sheet and signed Consent Form(s) must be given to the patient (see Appendices). The documents are available in electronic format from to facilitate printing onto local headed paper. Completed Consent Forms must not be sent to COG Trial staff. Original Consent Forms must be retained on site (it is recommended that the original is retained in the trial site file, with a copy filed in the relevant patient's hospital notes).

A Consent Notification Form must be sent to COG Trial staff with the Randomisation Form.

12.3 ETHICAL, REGULATORY AND SPONSOR REVIEW

COG Trial staff will submit the trial protocol and any amendments to main REC, MHRA and CTRG. The Principal Investigator must submit this protocol, any supporting documentation and any amendments, to a local ethics committee or similar body (LREC, R&D, etc.), as appropriate in accordance with local requirements and recommendations made by the main REC.

12.4 ANNUAL PROGRESS REPORT

COG Trial staff will send an annual trial update report to the main REC, which will be distributed to all sites. It is the responsibility of each site to send a copy of this report to their local R&D department in accordance with local requirements and recommendations made by the main REC. Any additional local information required by the committee must also be submitted. Additional data required by local committees are available from COG Trial staff on request.

12.5 PATIENT CONFIDENTIALITY

The personal data recorded on all documents will be regarded as confidential, and to preserve each patient's anonymity, only initials, date of birth and COG patient identifier will be recorded on the CRFs. The patient's name and NHS number (where available) will be collected once to allow flagging with The NHS Information Centre, in the UK, only if the site will allow and the patient has completed the relevant section of the Consent Form. The Principal Investigator must ensure the patient's anonymity is maintained.

The Principal Investigator must keep a separate log of patients' trial numbers, names, addresses and hospital numbers to enable patients to be tracked. The Principal Investigator must maintain documents not for submission to COG Trial staff (e.g. patients' completed Consent Forms), in strict confidence in a secure area.

OCTO will maintain the confidentiality of all patient data and will not reproduce or disclose any information by which patients could be identified, other than reporting of serious adverse events. Patients should be reassured that their confidentiality will be respected at all times.

COG Trial staff and authorised representatives from the Sponsor may need access to patient medical notes/records (source data) on-site during any monitoring or audit visits. An independent internal audit team, an AstraZeneca audit team and inspectors from regulatory body/bodies may visit the site and would require access to source data. In the case of specific problems and/or governmental queries, it will also be also necessary to have access to the complete trial records, provided that patient confidentiality is protected.

12.6 PATIENT WITHDRAWAL

Patients have the right to withdraw from the trial at any time for any reason. Investigators also have the right to withdraw patients from the trial. Full details of the reasons for withdrawal must be recorded on the relevant CRF(s). If patient is only withdrawn from trial treatment, they must be followed-up in accordance with the protocol. If a patient withdraws their consent to treatment and/or further follow-up, a Consent Withdrawal Form (see Appendices) must be completed. Copies are available from COG Trial staff upon request.

12.7 PROTOCOL AMENDMENTS

Any variation in procedure from that specified in the COG protocol may lead to the results of the trial being questioned and in some cases rejected. Any proposed protocol change must therefore be submitted in writing to OCTO to be pre-approved by the COG Steering Committee. All agreed protocol amendments will be documented by the trials office and will be submitted to the main REC for approval prior to submission to all LRECs. Changes not pre-approved by the COG Steering Committee will be considered as protocol deviations. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interests of individual patient.

12.8 INDEMNITY

COG is an investigator led and designed trial co-ordinated by the Oncology Clinical Trials Office (OCTO) in Oxford. The University of Oxford maintains Clinical Trials Insurance, which includes provision for "No Fault Compensation" together with Professional Liability/Professional Indemnity Insurance, and which, to the extent that a claim is made against the Sponsor, will apply to this study.

13 QUALITY ASSURANCE

13.1 PROTOCOL COMPLIANCE

All sites taking part in the trial will be required to attend a start-up meeting/investigator call to ensure compliance with the protocol and allow training on procedures and data collection methods. This will usually be carried out by telephone conference call, arranged by COG Trial staff.

All amendments to the protocol, procedures and other trial documentation must be submitted to the local ethics committee, in accordance with local procedures and recommendations made by the main REC. Submissions must be made and approval sought from other local parties (e.g. R&D Department) as required in accordance with local procedures.

COG Trial staff will monitor the compliance of sites taking part in the trial on an ongoing basis. Where non-compliance with the protocol or the standard procedures set out in the Clinical Trial Agreement is suspected, the Chief Investigator for the trial will contact the site to resolve any problems. If appropriate, the matter will be referred to the COG Trial Management Group at their next meeting or by correspondence with members if urgent.

The COG Trial Management Group has the full authority to take appropriate corrective action, including temporary or permanent withdrawal of the site from COG and other trials run by OCTO.

Sites and named Principal Investigators contributing to the COG Trial will be acknowledged on the final publication.

13.2 MONITORING AND AUDIT

CENTRAL MONITORING

Study sites will be monitored centrally by checking incoming forms for compliance with the protocol, data consistency, missing data and timing. All changes to data that could influence the outcome will be queried with and approved by the study site in a timely manner. For all other data, where there is no doubt about the source of any errors, clear changes to data will be made internally by OCTO staff without referring back to the study site. Study staff will be in regular contact with site personnel (by phone/fax/email/letter) to check on progress and deal with any queries that they may have including those arising from queries raised by the trials office.

ON-SITE MONITORING

Approximately 10% of participating sites will be visited by a member of the OCTO monitoring team according to an agreed monitoring plan. The Principal Investigator will allow the trial staff access to source documents as requested. Investigators and site staff will be notified in advance about any planned monitoring visits.

AUDIT

A random sample of approximately 10% of patients entered into COG may be audited by an independent internal audit team, CTRG or by AstraZeneca if requested. The Principal Investigator will allow the trial staff access to source documents as requested. Sites will be notified of an audit in advance.

INSPECTION

If a site is notified of an inspection relating to the COG trial by a regulatory or other official body, the site staff must notify COG Trial staff immediately.

14 TRIAL MANAGEMENT AND TRIAL COMMITTEES

COG will be coordinated from OCTO in Oxford. Responsibilities of the trial personnel and committees are as follows:

- The Chief Investigator (CI) and OCTO are responsible for the day-to-day running of the trial.
- The Trial Management Group (TMG) will consist of the Chief Investigator, other lead investigators (clinical and non-clinical), members with specific interests (e.g. pharmacist; nurse; user representative) and members of OCTO. The TMG will be responsible for the management of the trial.
- The Trial Steering Committee (TSC) provides overall supervision for the trial and provides advice through its independent Chairman. The TSC will meet at least annually, and will receive reports from OCTO, and TMG. The ultimate decision for the continuation of the trial lies with the TSC.
- The Data and Safety Monitoring Committee (DSMC) will be provided with data concerning recruitment and toxicity. The DSMC will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant trials, justifies the continuing recruitment of further patients. The committee will meet 6 monthly during the recruitment phase of the trial. The DSMC may recommend discontinuation of the trial if the recruitment rate or data quality are unacceptable or if there are cases of excessive toxicity. The DSMC may recommend stopping the trial early if any requested interim analyses show differences between treatments that would be deemed to be convincing to the clinical community.

15 STUDY ADMINISTRATION

The University of Oxford is registered under the Data Protection Act (1998) for the purpose of research and statistical analysis (health), registration number Z575783X (for more details contact COG Trial staff).

15.1 COMPUTERISED RECORDS

Create data - Details of study sites and participating staff will be recorded during the study. Patient data records will be created at randomisation and data entered from CRFs during follow up.

Modify and maintain data - Records of study sites and participating staff will be modified to maintain accurate details of personnel and status. Data from CRFs will be modified to correct any erroneous or missing entries. The reason for these changes will be recorded in an audit trail.

Archive - At the conclusion of the trial when all patient data has been collected and the analysis is complete, all data stored on the computer system will be archived. After trial conclusion, if any audit is required or new analysis to be performed, the data will be retrieved.

Transmit - Such data as required to execute remote randomisations may be transmitted from approved sites by staff with authorised access.

15.2 PUBLICATION AND INTELLECTUAL PROPERTY

The COG Trial Management Group (TMG) is responsible for approving the content and distribution of all publications, abstracts and presentations arising from the trial and for assuring the confidentiality and integrity of the trial. The TMG will provide collaborators with approved publicity material and information updates at regular intervals during the course of the trial. The definitive publications from COG will be written with input from the collaborative group(s) and will acknowledge all those who have contributed to the trial.

For these reasons, individuals wishing to present or publish material arising from COG should not do so without the written approval of the TMG. All authors must agree to submit a copy of any manuscript and/or abstract for review and comment by the TMG at least sixty (60) days prior to its submission for publication. The TMG will respond with any requested revisions and authors must agree to delete any confidential information and make any corrections of fact before submitting the document for publication. If requested the TMG will take reasonable steps to expedite the review process to meet the author's publication deadlines. Such approval will not be forthcoming until the unblinded, multi-centre trial results have been published.

The data arising from COG will belong to the University of Oxford and the TMG shall act as custodian of these data.

15.3 ARCHIVING

All source and study documentation must be securely retained by the Investigator for at least two years after the last approval of a marketing application in an ICH (International Conference on Harmonisation) region and until there are no pending or contemplated marketing applications, or at least 15 years, whichever is the longer. OCTO will archive the TMF for a minimum of 5 years and sites will be responsible for their own archiving according to local procedures.

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APPENDIX 1. PATIENT INFORMATION SHEET

COGPISV5.0_03Aug2010

To be printed on hospital/Trust headed paper

Title:	**UK PATIENT INFORMATION SHEET** **Cancer Oesophagus Gefitinib (COG) Trial** ISRCTN: 29580179 EudraCT: 2007-005391-13

You are invited to take part in a research study. Before you decide whether you wish to take part, it is important that you understand why the research is being done and what it will involve. Your doctor and/or nurse will discuss the study with you and allow you time to ask any questions you may have. This information sheet is designed to help you understand what the study is about and you may take this sheet away with you. (Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study*).* Please take time to read through the following information carefully and discuss it with others if you wish. Please ask if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Taking part in this study is entirely voluntary

PART 1

What is the purpose of the study?

You have been diagnosed at gastroscopy and biopsy as having oesophageal cancer. This is a change in the lining of the lower gullet (oesophagus) where normal tissue has become cancerous.

The management of oesophageal cancer varies. Following one course of chemotherapy for advanced disease there is no alternative treatment likely to produce benefit. The aim of the trial is to investigate the benefits of Iressa® (gefitinib), which at present is an unlicensed drug, in halting or slowing the progression of oesophageal cancer (adenocarcinoma and squamous cancers). We believe that this therapy has the potential to be very important in managing the disease but at present it is not known if this is true. There is evidence already that gefitinib (Iressa®) is effective in other cancers. A small study looking at oesophageal cancer patients both with adenocarcinoma and squamous cancer of the gullet showed a 10% to 15% decrease in tumour size.

Why have I been chosen?

As a patient with oesophageal cancer (adenocarcinoma or squamous cancer), you have been chosen because you are aged over 18 years of age and you have this disease. You may be suitable for treatment within this study.

Do I have to take part?

You will be given time to consider taking part in the study. **Participation in the trial is entirely voluntary.** Your standard of care will not be affected if you decide not to take part in this study.

If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. You will also be given a copy of the signed consent form to keep. You are free to withdraw at any time and without giving a reason. This will not in any way affect any future care you will receive from your medical and nursing team.

Your participation in this study may be stopped at any time without your consent, either by the study doctor or study Co-Sponsors (University of Oxford/Royal Wolverhampton Hospitals NHS Trust), after the reason(s) for doing so have been explained to you, and after you have been given advice about continued care for your condition, if this is appropriate.

What will happen to me if I take part?

If you agree to take part in the study, you will be randomised (decided by chance) to one of two treatment groups (treatment arms) for several months. One group will receive active treatment (gefitinib) and the other will receive placebo treatment (dummy tablet). You will take two tablets, once a day with or without food. Neither you nor your treating doctor will know which treatment group you will be allocated to.

Treatment Arms

Treatment A: Gefitinib (Iressa®), 500mg (2 x 250mg tablets) once a day

Treatment B: Placebo, two tablets, once a day

If you agree, information held by the NHS Information Centre may be used to follow up your health status.

What will I have to do?

You will be required to take the medicine every day for a period of three months, or longer if you receive any benefit. There are no dietary or lifestyle restrictions. You can continue to drive, drink alcohol, and take part in sport. You should continue to take any other regular medicine. During your hospital visits, you should tell your doctor about any other medications you are taking.

You will be required to come to the hospital to see your doctor/nurse at the start of the study and then every 4 weeks for the first 4 months and then every 8 weeks until the study ends. During these hospital visits your doctor/nurse will examine you, take blood samples and you will have a CT scan done.

You will be asked to complete two Quality of Life (QoL) questionnaires at a maximum of four different time points – prior to starting treatment; 4 weeks after starting treatment; 8 weeks after starting treatment and 12 weeks after starting treatment. This will help us to assess health-related quality of life issues. At each point, the questionnaires will take about 10 to 15 minutes to complete. If you withdraw from study treatment, you will not be required to complete any further questionnaires.

All information will be kept confidential and you will not be identified by name.

What is the drug being tested?

The drug is called gefitinib (Iressa®). This drug seems to block molecules on the outside of the cancer cells from stimulating growth. Drugs like these have been available for five years and are being used by many thousands of patients in trials.

What are the alternatives for treatment?

You do not have to take part in this study to receive treatment for your condition. You may choose not to take part in this study or you may discontinue your participation at any time and your standard of care will not be affected. Instead of participating in this study, there may be other treatment options available to you. The currently accepted standard of best medical practice for second-line therapy, i.e. those not responding or not suitable for first-line therapy, is uncertain. Patients are sometimes given chemotherapy, sometimes radiotherapy, and sometimes given palliation with oesophageal stents (which are placed in the gullet to keep the food pipe open). You should discuss with your doctor the potential advantages/disadvantages and benefits/risks of other treatments.

What are the possible side effects of any treatment received when taking part?

The study medications may cause some side effects but these are usually mild to moderate and reversible. Do not be alarmed by the list below, as it is unlikely that you will experience all of these side effects. You may experience none or only some. Contact your doctor **promptly** if any of the following happen to you, as you may need further examination or treatment. In addition your doctor may need to stop the study medication.

VERY COMMON SIDE EFFECTS (more than 1 in every 10 patients is likely to have them)	• Diarrhoea • Nausea (feeling sick) • Acne-like skin reactions that can be itchy, dry and red
COMMON SIDE EFFECTS (between 1 in 10 and 1 in 100 is likely to have them)	• Vomiting • Loss of appetite • Red and sore mouth • Nail problems • Loss of hair • Weakness • Conjunctivitis (red and itchy eye) • Red and sore eyelid • Dehydration and changes in blood tests looking at liver function • Inflammation of the lungs - called Interstitial Lung Disease (ILD), has been reported commonly (1.1%) in patients receiving gefitinib with some patients dying from this condition. If you experience symptoms such as sudden breathlessness or cough (possibly with a fever), or if any breathlessness or cough you already have suddenly becomes worse (again possibly with a fever), you **must** tell your doctor straight away. He or she may need to do some tests and may need to stop your study medication
UNCOMMON SIDE EFFECTS (between 1 in 100 and 1 in 1000 patients is likely to have them)	• Inflammation of the pancreas • Inflammation of the liver • Allergic reactions • Other eye problems such as ulcers on the surface of the eye (cornea), sometimes associated with in-growing eyelashes and changes in the way your blood clots
RARE SIDE EFFECTS (less than 1 in every 1000 patients is likely to have them)	• Include symptoms such as very severe pain in the upper part of the stomach area and severe nausea (feeling sick) and vomiting • Extremely severe skin reactions consisting of skin sloughing possibly with involvement of the lips and mucous membranes

What are the possible disadvantages and risks of taking part?

There are risks related to drug treatment as detailed above. There may be risks involved in taking this medication that have not yet been identified. In a 2 year study involving rats, some rats that received the highest dose of gefitinib developed benign liver growths, and some females developed a cancer in lymph nodes. It is not known whether these results in rats apply to people. There is always a risk involved in taking a new medication but every precaution will be taken and you are encouraged to report anything that is troubling you. You should tell your doctor immediately if you develop any unusual symptoms.

If you are a female, able to have children and are sexually active, or if you are a male and are sexually active, you must agree to use reliable birth control methods during your participation in this study. It is important that you or your partner do not become pregnant whilst taking the study treatment.

There is a possibility that taking part in this study may affect any private medical insurance that you may have. If you are at all worried about this, please contact your insurance company.

Ionising Radiation (Medical Exposure) Regulations – IRMER

This study requires you to have CT scans to work out if the study medication is helping you. If your cancer is stabilized or gets smaller then you may continue to take the study medication, but if the cancer is getting worse then the study medication will stop because clearly it is not helping. On average patients in this study will have 3 CT scans, which involves exposure to a small amount of X-ray radiation. The risk of harm from this dose of radiation is small, and regarded as equivalent to a few years of natural background radiation. The risk from the radiation received means that if 1000 patients took part then by 10 years there would be 1 additional cancer caused by the CT scans given. This risk is tiny in comparison to the seriousness of your disease.

What are the possible benefits of taking part?

You will receive the benefit of health information and a chance to be in a research study, the results of which may benefit other patients with similar tumours or other cancers in the future.

What if new information becomes available?

Sometimes during the course of a research project, new information becomes available about the drug that is being studied. If this happens, your doctor will tell you about it, provide you with written information and discuss whether you want to continue in the study. If you decide to withdraw from treatment, your doctor will make arrangements for your care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

On receiving new information your doctor may consider it to be in your best interests to withdraw you from the study treatment. Your doctor will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

When your treatment and study follow-up comes to an end, your doctors will see you regularly for follow up in their outpatient clinics, according to their usual routine.

PART 2

What will happen if I don't want to carry on with the study?

We would recommend that you finish the course of treatment, however, participation in the study is voluntary and you may leave the trial at any time without giving reasons and without affecting your future care. If you do not wish to have further information about you during follow-up, you will be asked to sign a Consent Withdrawal Form.

What if there is a problem?

You will receive the standard medical care available during and after the trial, but because these are still relatively new treatments, unexpected side effects may occur. In the unlikely event of an injury arising from taking part in this trial, you will be provided with the necessary care.

If you are harmed and this is due to someone's negligence then you may have grounds for legal action for compensation against the University of Oxford (in respect of any harm arising out of the participation in the Clinical Trial) or the NHS (in respect of any harm which has resulted from any clinical procedure being undertaken). Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during

the course of this study, the normal National Health Service complaints procedure mechanisms may be available to you. Your doctor will give you further information if necessary.

Will my taking part in this study be kept confidential?

Information collected about you during the trial will be kept by the Oncology Clinical Trials Office (OCTO) on behalf of the University of Oxford/Royal Wolverhampton Hospitals NHS Trust (the study Sponsors), or their representatives. This information is strictly confidential.

If you agree, information held by the NHS and records maintained by the NHS Information Centre may be used by the Sponsor to follow up your health status. This would involve forwarding your name and NHS number to OCTO. If you choose for this not to happen, it will not prevent you from entering into the trial.

Occasionally, at any time during or after the study the Sponsor or the Sponsor's representatives, representatives from your treating hospital, the regulatory agency who authorised the trial, and the company Astra Zeneca who are providing the drugs for the trial, might monitor or audit the trial and might need to access your medical records, which identify you by name. This is to ensure that the study is being carried out correctly. Any information that leaves the hospital, for this particular purpose will have your name and address removed so that you cannot be recognised from it.

Some of the results of the study may be presented outside the European Union and these areas may have fewer rules about data protection. However you would never be identified individually during these presentations. Data sent to other groups in the UK and abroad will not include information that identifies you by name (your trial number will be used only) and agreements will ensure that the data is treated confidentially. Identifiable information about you will only be sent once (encrypted) to the NHS Information Centre to ensure accuracy of follow-up data.

Your GP and any other doctors who may treat you, but who are not involved in the study, will be notified that you are taking part in the study.

What will happen to the results of the research study?

Results of the trial are likely to be published in medical journals, used for scientific presentations and may also be forwarded to health authorities worldwide. The confidentiality of all patients will be maintained. You will not be identified in any reports or publications resulting from the study. If you would like to obtain a copy of the published results, please ask your doctor.

The results of the study may be used by the researchers to change standard treatment for patients with cancer of the digestive tract, which may be of commercial benefit to the manufacturers of the drugs used.

Who is organising and funding the research?

The trial is funded by Cancer Research UK (CRUK) and organised and managed by the Oncology Clinical Trials Office (OCTO) on behalf of the Sponsors (University of Oxford/Royal Wolverhampton Hospitals NHS Trust). Gefitinib (Iressa®) and placebo are supplied by the manufacturing and pharmaceutical company, AstraZeneca.

The doctor conducting the research is not paid for including patients in the study. The costs are borne by the NHS.

Who has reviewed the study?

The study has been reviewed by the Cancer Research UK, approved by the Berkshire Research Ethics Committee (REC Reference: 08/H0505/127), one of the national research ethics committees in the UK, and the Medicines and Healthcare products Regulatory Agency (MHRA), UK.

What if I have more questions or haven't understood something?

Please feel free to ask any further questions of the doctors and nurses looking after you before deciding to take part in the trial or at any time during the study. If you would like further information about clinical trials, it is available at the following website: http://www.cancerbackup.org.uk/Trials/Understandingtrials

Your local contact is: _____ **Tel:** _____

Independent contact is: _____ **Tel:** _____

Thank you for reading this information sheet

To be printed on hospital/Trust headed paper

Patient Consent Form A: Study Participation

Title: **Cancer Oesophagus Gefitinib (COG) Trial**

ISRCTN: 29580179 EudraCT: 2007-005391-13

Study Doctor Name:		**Study Site:**			
Patient Name:					
Relating to Patient Information Sheet	**Version No.:**		**Version Date:**	___/___/_____	

Patient Statement and Signature ***to be completed by the patient***

Please **initial** the boxes below if you agree

	Initials
1. I have read and received a copy of the COG Patient Information Sheet and I fully understand what is involved in taking part in this trial and have had an opportunity to ask questions, and all of my questions have been answered.	
2. I understand that my participation is voluntary and that I am free to withdraw from the study at any time without giving a reason and without my medical care or legal rights being affected	
3. I give my permission for information held by the NHS and records maintained by the NHS Information Centre to be used to keep in touch with me and follow up my health status. This includes my name and NHS number being sent to the Oncology Clinical Trials Office (OCTO).	
4. I also understand that relevant sections of my medical notes may be looked at by responsible individuals from the Oncology Clinical Trials Office (OCTO) or other authorised representatives from the University of Oxford & Royal Wolverhampton Hospitals NHS Trust – Co-Sponsors, representatives from my treating hospital, AstraZeneca (manufacturer of gefitinib & placebo) and the regulatory agency who authorised the trial. I give permission for these individuals to have access to my medical records which identify me by name.	
5. I understand that I will not be identified in any reports or publications resulting from the study	
6. I also understand that some of this research will be carried out with companies who may use the information for commercial gain.	
7. I give my permission for a letter and information about the COG trial to be sent to my General Practitioner, which will tell him/her that I have decided to take part in the study.	
8. I voluntarily agree to participate in this study.	

Your signature confirms that you have had an opportunity to ask questions and that all of your questions have been answered. [You will be given a signed and dated copy of this consent form to take away with you]

Patient signature:		Name (print):		Date signed:	___/___/_____

Investigator Statement and Signature ***To be completed by the person taking consent***

I have discussed this clinical research study with the patient and/or his or her authorised representative using a language that is understandable and appropriate. I believe that I have fully informed the participant of the nature of this study and the possible benefits and risks of taking part. I believe the participant has understood this explanation.

Signature:		Name (print):		Date signed:	___/___/_____

APPENDIX 3. GP LETTER

COGGPL_V4.0_15Apr2010

To be printed on hospital headed paper

Re: Cancer Oesophagus Gefitinib (COG) Trial

Dear Doctor,

Your patient, ... has kindly agreed to take part in this trial. The aim is to determine if gefitinib (Iressa®) which is an EGFR inhibitor can slow down or halt the progression of oesophageal cancer (adenocarcinoma and squamous cancers). As you are aware, oesophageal carcinoma is a highly progressive disease, and there are no second-line therapies once conventional chemotherapy or radiotherapy has failed. This patient has been randomised to one of two arms, a placebo or an active drug. The reason we have to use a placebo arm is that the evidence for efficacy in these drugs has not yet been proven conclusively. This is a placebo-controlled study, so the patient will not know what medication they are taking. They will be provided with their allocated medication.

Your patient will be followed up in the oncology clinic on a monthly basis. Disease progression or intolerable side effects will result in the patient discontinuing trial medication. However they will continue to be followed up.

So far approximately 5,000 patients have received gefitinib (Iressa®) in clinical trials and it has been approved by a number of regulatory authorities. These include the European Medicines Evaluation Agency. Gefitinib (Iressa®) is shown to be well tolerated and associated with few incidents of side-effects. Some patients (between 1%-10%) will complain of rash or nausea. Some (less than 2%) will have more serious side-effects such as abnormal blood tests. Interstitial Lung Disease (ILD) or inflammation of the lungs is also commonly reported (1.1%) with some patients dying from this condition.

There is always a risk in taking a new medication but every precaution will be taken, and patients will be encouraged to report anything that is troubling them.

Please find enclosed a copy of the Patient Information Sheet.

Please contact the COG Trial staff at OCTO (Oncology Clinical Trials Office) on Tel: +44 (0)1865 617016 or via Email: cog@octo-oxford.org.uk, if you have any objection to the trial or if you require further information.

Yours sincerely,

Enclosed: COG Patient Information Sheet

APPENDIX 4. SIDE EFFECTS ASSOCIATED WITH GEFITINIB

Very common (>10%)	*Digestive:*	▪ Diarrhoea, mainly mild or moderate in nature (CTCAE grade 1 or 2) and, less commonly, severe (CTCAE grade 3 or 4).
		▪ Nausea, mainly mild in nature (CTCAE grade 1).
	Skin and appendages:	▪ Skin reactions, mainly a mild or moderate (CTCAE grade 1 or 2) pustular rash, sometimes itchy with dry skin, on an erythematous base.
Common (>1 - ≤10%)	*Digestive:*	▪ Vomiting, mainly mild or moderate in nature (CTCAE grade 1 or 2).
		▪ Anorexia, mild or moderate in nature (CTCAE grade 1 or 2).
		▪ Stomatitis, predominantly mild in nature (CTCAE grade 1).
		▪ Dehydration, secondary to diarrhoea, nausea, vomiting or anorexia.
		▪ Dry mouth*, predominantly mild in nature (CTCAE grade 1)
	Haemic and lymphatic:	▪ Haemorrhage, such as epistaxis and haematuria
	Metabolic and nutritional:	▪ Liver function abnormalities, consisting mainly of mild or moderate elevations in transaminases (CTCAE grade 1 or 2).
		▪ Asymptomatic laboratory elevations in blood creatinine
	Skin and appendages:	▪ Nail disorder
		▪ Alopecia
	Whole body:	▪ Asthenia, predominantly mild in nature (CTCAE grade 1).
		▪ Pyrexia
	Ophthalmological:	▪ Conjunctivitis, blepharitis, and dry eye*, mainly mild in nature (CTCAE grade 1).
Uncommon (>0.1 - ≤1%)	*Haemic and lymphatic:*	▪ INR elevations and/or bleeding events in some patients taking warfarin
	Ophthalmological:	▪ Corneal erosion , reversible and sometimes in association with aberrant eyelash growth
	Respiratory:	▪ Interstitial lung disease, often severe (CTCAE grade 3-4)*. Fatal outcomes have been reported.
Rare (>0.01 - ≤0.1%)	*Digestive:*	▪ Pancreatitis
		▪ Hepatitis
Very rare (<0.01%)	*Skin and appendages:*	▪ Allergic reactions, including angioedema and urticaria
		▪ Toxic epidermal necrolysis, Stevens Johnson syndrome and erythema multiforme

*This event can occur in association with other dry conditions (mainly skin reactions) seen with gefitinib. Based on data from worldwide clinical studies, expanded access/compassionate use and post-marketing use, the estimated reporting rate of ILD-type events overall is approximately 0.3% outside of Japan and approximately 3% in Japan.

From a phase III double blind clinical trial (1692 patients) comparing gefitinib plus best supportive care (BSC) to placebo plus BSC in patients with advanced NSCLC who had received 1 or 2 prior chemotherapy regimens and were refractory or intolerant to their most recent regimen, the incidence of ILD-type events in the overall population was similar, and approximately 1% in both treatment arms. The majority of ILD-type events reported were from patients of oriental ethnicity and the ILD incidence among patients of oriental ethnicity receiving gefitinib therapy and placebo was similar, approximately 3% and 4% respectively. One ILD-type event was fatal, and this occurred in a patient receiving placebo.

In a Post-Marketing Surveillance study in Japan (3350 patients) the reported rate of ILD-type events in patients receiving gefitinib was 5.8%.

In a Japanese Pharmacoepidemiological case control study (see section 4.4) in patients with NSCLC, the cumulative incidence of ILD at 12 weeks follow-up was 4.0% in patients receiving gefitinib and 2.1% in those receiving chemotherapy and the adjusted odds ratio (OR)of developing ILD was 3.2 (95% confidence interval (CI)1.9 to 5.4) for gefitinib versus chemotherapy. An increased risk of ILD on gefitinib relative to chemotherapy was seen predominantly during the first 4 weeks of treatment (adjusted OR 3.8; 95% CI 1.9 to 7.7); thereafter the relative risk was lower (adjusted OR 2.5; 95% CI 1.1 to 5.8).

APPENDIX 5. COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

Full listings of version 3.0 can be obtained from COG Trial staff or from: http://ctep.cancer.gov/reporting/ctc.html

Adverse Event	Grade				
	1	2	3	4	5
Alopecia	Thinning or patchy	Complete	_____	_____	____
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual vacuation needed	Life threatening consequences (e.g. obstruction, toxic megacolon)	Death
Diarrhoea Includes diarrhoea of small bowel or colonic origin, and/or ostomy diarrhoea	Increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline	Increase of 4-6 stools/day over baseline; IV fluids indicated <24 hrs; moderate increase in ostomy output compared to baseline; not interfering with ADL	Increase of ≥7 stools/day over baseline; incontinence; IV fluids ≥24 hrs; hospitalisation; sever increase in ostomy output compared to baseline; interfering with ADL	Life threatening consequences (e.g. haemodynamic collapse)	Death
Fatigue (lethargy, malaise, asthenia)	Mild fatigue over baseline	Moderate or causing difficulty performing some ADL	Severe fatigue interfering with ADL	Disabling	____
Haemoglobin (Hgb)	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	8.0 - <10.0 g/dL 80 - <100 g/L 4.9 - <6.2 mmol/L	6.5 - <8.0 g/dL 65 - <80 g/L 4.0 - <4.9 mmol/L	<6.5 g/dL <65 g/L <4.0 mmol/L	Death
Haemorrhage, GI (select: Abdomen NOS, anus, bleary treem caecum/appendix, colon, duodenum, oesophagus, ileum, jejunum, liver, lower GI NOS, oral cavity, pancreas, peritoneal cavity, rectum, stoma, stomach, upper GI NOS, varices (oesophageal), varices (rectal)	Mild, intervention (other than iron supplements) no indicated	Symptomatic and medical intervention or minor cauterisation indicated	Transfusion, interventional radiology, endoscopic, or operative intervention indicated; radiation therapy (i.e. haemostasis of bleeding site)	Life-threatening consequences; major urgent intervention required	Death
Mucositis/stomatitis (functional/ symptomatic)	Upper aerodigestive tract sites: Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function Lower GI sites: Minimal discomfort, intervention not indicated	Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with function but not interfering with ADL Lower GI sites: Symptomatic, medical intervention indicated but not interfering with ADL	Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL Lower GI sites: Stool incontinence or other symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Mucositis/stomatitis (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life threatening consequences	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated <24 hrs	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥24 hrs	Life threatening consequences	Death
Neutrophils/ granulocytes (ANC/AGC)	<LLN - 1.5 x 10^9 /L <LLN - 1500/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 <500/mm^3	Death
Platelets	<LLN – 75.0 x 10^9 /L	≥50.0 - <75.0 x 10^9 /L	≥25.0 - <50.0 x 10^9 /L	<25.0 x 10^9 /L	Death

	<LLN – 75,000/mm^3	≥50,000 - <75,000/mm^3	≥25,000 - <50,000/mm^3	<25,000/mm^3	
Pruritis/itching	Mild or localised	Intense or widespread	Intense or widespread and interfering with ADL	____	____
Rash: acne/acneiform	Intervention not indicated	Intervention indicated	Associated with pain, disfigurement, ulceration or desquamation	____	Death
Vomiting	1 episode in 24 hrs	2-5 episodes in 24 hrs; IV fluids indicated <24 hrs	≥6 episodes in 24 hrs; IV fluids, or TPN indicated ≥24 hrs	Life-threatening consequences	Death

Key: WNL Within normal limits LLN Lower limit of normal ADL Activities of daily living

APPENDIX 6. COCKCROFT- GAULT FORMULA

FOR CALCULATING GLOMERULAR FILTRATION RATE

The estimated GFR is given by:

$$\text{Males} = \frac{1.25 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$$

$$\text{Females} = \frac{1.05 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine } (\mu\text{mol/l})}$$

APPENDIX 7. STAGING OF OESOPHAGEAL CANCER

STAGING

Stage	T	N	M
0	Tis	0	0
I	1	0	0
IIA	2 or 3	0	0
IIB	1 or 2	1	0
IIIA	3	1	0
	4	1	0
IV	Any	Any	1
IVA	Any	Any	1a
IVB	Any	Any	1b

DEFINITIONS

Primary tumour (T)

TX Tumour proven by the presence of malignant cells but not visualized by roentgenography or endoscopy, or any tumour that cannot be assessed in pre-treatment staging

T0 No evidence of primary tumour

TIS Carcinoma in situ.

T1 Tumour invades lumina propria

T2 Tumour invades muscularis propria

T3 Tumour invades adventitia

T4 Tumour invades adjacent structures

Nodal Involvement (N)

NX Regional nodes cannot be assessed

N0 No demonstrable metastasis or regional lymph nodes

N1 Regional node metastasis

Distant Metastasis (M)

M0 No known metastasis

M1 Distant metastasis present - specify site(s)

M1a Tumours of lower oesophagus celiac nodes; tumours of upper oesophagus cervical nodes

Tumours of mid oesophagus not applicable

M1b Other distant metastases

Reference: American Joint Commission on Cancer. AJCC staging manual 6th Edition, Springer Verlag, New York 2002, page 91

APPENDIX 8. WHO PERFORMANCE STATUS

Status	Description
0	Asymptomatic, fully active and able to carry out all pre disease performance without restrictions
1	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance activity of a light or sedentary nature
2	Symptomatic, ambulatory and capable of self-care but unable to carry out any work activities. Up and about 50% of waking hours: in bed less than 50% of the day
3	Symptomatic, capable of only limited self care, confined to bed or chair more that 50% of waking hours, but not bed ridden

APPENDIX 9. RECIST CRITERIA

The following contains excerpts from the recently published RECIST criteria. For more information, a full copy can be seen at http://www.eortc.be

Ref. P. Therasse, S. A. Arbuck, E. A. Eisenhauer et al,., New Guidelines to evaluate the response to treatment in solid tumors. Journal Of the National cancer institute Vol 92, No 3, Feb2, p 205.

The selected sections are named as in the full RECIST document.

Section 2 MEASURABILITY OF TUMOUR LESIONS AT BASELINE

2.1 Definitions

At baseline, tumour lesions will be categorised as follows: measurable (lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as 20 mm with conventional techniques or as 10 mm with spiral CT scan [*see* section 2.2]) or nonmeasurable (all other lesions, including small lesions [longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan] and truly nonmeasurable lesions).

The term "evaluable" in reference to measurability is not recommended and will not be used because it does not provide additional meaning or accuracy.

All measurements should be recorded in metric notation by use of 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 treatment.

Lesions considered to be truly nonmeasurable include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

(*Note:* Tumour lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered must be defined in the protocol when appropriate.)

Section 3 TUMOUR RESPONSE EVALUATION

3.1 Baseline evaluation

3.1.1 Assessment of overall tumour burden and measurable disease

To assess objective response**,** it is necessary to estimate the overall tumour burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion (as defined in section 2.1). If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

3.1.2 Baseline documentation of "target" and "nontarget" 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 (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum longest diameter. The baseline sum longest diameter will be used as the reference by which to characterise the objective tumour response**.**

All other lesions (or sites of disease) should be identified as nontarget 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.

3.2 Response criteria

3.2.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumour response for target lesions. The criteria have been adapted from the original WHO Handbook, taking into account the measurement of the longest diameter only for all target lesions: complete response—the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of

target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

3.2.2 Evaluation of nontarget lesions

This section provides the definitions of the criteria used to determine the objective tumour response for nontarget lesions: complete response—the disappearance of all nontarget lesions and normalisation of tumour marker level; incomplete response/stable disease—the persistence of one or more nontarget lesion(s) and/or the maintenance of tumour marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions.

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

3.2.3 Evaluation of best overall response

The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease 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 (see section 3.3.1). Table provides overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions.

(Notes:

- 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 disease progression, even after discontinuation of treatment.
- Conditions that may define early progression, early death, and in-evaluability are study specific and should be clearly defined in each protocol (depending on treatment duration and treatment periodicity).
- 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 aspiration/biopsy) before confirming the complete response status.)

Table 1. Overall responses for all possible combinations of tumour responses in target and nontarget lesions with or without the appearance of new lesions*

Target lesions	Nontarget 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

CR = complete response; PR = partial response; SD = stable disease; and PD = progressive disease. *See* text for more details.

Section 5 REPORTING OF RESULTS

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response**,** 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). (*Note:* By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.)

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Sub analysis may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g. early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, this sub analysis may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should be provided.

COG

EORTC QLQ-C30 (version 3)

Site:	Investigator:	
Trial Number: CG__ __ __ __ __	Patient Initials:	Date of Birth: dd|mon|yyyy

Visit (please circle appropriate time point)	Baseline	Visit 2	Visit 3	Visit 4

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at all	A little	Quite a bit	Very much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

COG

EORTC QLQ-C30 (version 3)

Site:	Investigator:	
Trial Number: CG__ __ __ __ __	Patient Initials:	Date of Birth: dd|mon|yyyy

During the past week:	Not at all	A little	Quite a bit	Very much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Patient to please initial and date below on completing this form:

Patient Initials: _____ **Date:** dd \|Mon \|yyyy

APPENDIX 11. QUALITY OF LIFE QUESTIONNAIRE – EORTC QLQ - OG25

EORTC QLQ – OG25

Site:	Investigator:	
Trial Number: CG__ __ __ __ __	Patient Initials:	Date of Birth: dd|mon|yyyy

Visit (please circle appropriate time point)	Baseline	Visit 2	Visit 3	Visit 4

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
1. Have you had problems eating solid foods?	1	2	3	4
2. Have you had problems eating liquidised or soft foods?	1	2	3	4
3. Have you had problems drinking liquids?	1	2	3	4
4. Have you had trouble enjoying your meals?	1	2	3	4
5. Have you felt full up too quickly after beginning to eat?	1	2	3	4
6. Has it taken you a long time to complete your meals?	1	2	3	4
7. Have you had difficulty eating?	1	2	3	4
8. Have you had acid indigestion or heartburn?	1	2	3	4
9. Has acid or bile coming into your mouth been a problem?	1	2	3	4
10. Have you had discomfort when eating?	1	2	3	4
11. Have you had pain when you eat?	1	2	3	4
12. Have you had pain in your stomach area?	1	2	3	4
13. Have you had discomfort in your stomach area?	1	2	3	4
14. Have you been thinking about your illness?	1	2	3	4
15. Have you worried about your health in the future?	1	2	3	4
16. Have you had trouble with eating in front of other people?	1	2	3	4
17. Have you had a dry mouth?	1	2	3	4
18. Have you had problems with your sense of taste?	1	2	3	4
19. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
20. Have you had difficulty swallowing your saliva?	1	2	3	4
21. Have you choked when swallowing?	1	2	3	4
22. Have you coughed?	1	2	3	4
23. Have you had difficulty talking?	1	2	3	4
24. Have you worried about your weight being too low?	1	2	3	4
25. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

Patient to please initial and date below on completing this form:
Patient Initials: _____ Date: dd \|mon \|yyyy

APPENDIX 12. COG CONSENT WITHDRAWAL FORM

COGConsentWithdrawalFormV1.0_08Jul2008

To be printed on hospital/Trust headed paper

Consent Withdrawal Form

Cancer Oesophagus Gefitinib (COG) Trial

ISRCTN: 29580179 EudraCT: 2007-005391-13

Study Doctor Name:		**Study Site:**	
Patient Name:		**Trial No.:**	**CG** __ __ __ __

Patient Statement and Signature ***To be completed by the patient***

I wish to withdraw from the COG study. I no longer permit any information from my medical records to be used to obtain information for this study. This will apply for all records made on or after the date of this form. [Your doctor will need to notify the COG Trial Office of your withdrawal].

Please initial the boxes below if you agree

1. I wish to withdraw consent to using any data gathered on or after the date of this form. I understand that unless otherwise stated under 2 below, data collected prior to this date may still be used by responsible individuals taking part in the research. I understand that withdrawing from the study will not affect my medical care or legal rights.	
I wish to withdraw from further trial-related follow-up	
I wish to withdraw consent to using any tissue samples*	
I wish to withdraw consent to using blood samples I have given*	

*Samples collected prior to the date of this form will be destroyed

Your participation in COG means that we have already gathered some data. We would like to use this information in the future for analysing this trial and for future research. However, if you do not wish this information to be used, please complete the following section:

2. I wish to withdraw consent to using any data gathered prior to the date of this form	

The Investigator has discussed the withdrawal from the clinical research study with me, using a language that is understandable and appropriate. I have had the opportunity to ask questions.

Patient signature:		**Name (print):**		**Date signed:**	___/___/_____

Investigator Statement and Signature ***To be completed by the person taking consent***

I have discussed the withdrawal from the clinical research study with the patient, using a language that is understandable and appropriate. The patient has had the opportunity to ask questions.

Signature:		**Name (print):**		**Date signed:**	___/___/_____

The completed Consent Withdrawal Form must be kept in the COG site file, a copy given to the patient and copy filed in hospital notes

OCTO must be informed in writing of consent withdrawal by submission of a Consent Withdrawal Notification Form [Consent Withdrawal Form must not be sent to OCTO]

APPENDIX 13. COG ASSESSMENT FORMS – COMPLETION TIMELINES

CRFs/FORMS	TIMELINES FOR COMPLETION
ADDITIONAL DATA FORM	Please complete if more space is required to submit additional information with any COG trial form, post original to OCTO* within 1 month.
ADVERSE REACTION (AR) /TOXICITY FORM	Please complete when patient experiences an AR/toxicity (**CTCAE Grade 2, 3 and 4 only**), all AR/toxicities are to be recorded up to 30 days post the end of treatment. Post original to OCTO* within 1 month after 30 days from the end of treatment.
BASELINE/TREATMENT HISTORY FORM	Please complete at Baseline Visit, post original to OCTO* within 1 month.
DRUG DESTRUCTION FORM	Please complete for all drug destructions, fax to OCTO and post original to OCTO* at the completion of trial.
DRUG DISPENSING LOG	Please complete for all study treatment dispensed, post original to OCTO* within 1 month of the end of treatment.
END OF TREATMENT FORM	Please complete if patient has either **completed** or **permanently discontinued** study treatment, post original to OCTO* within 1 month.
HRQL FORMS (EORTC QLQ-C30, EORTC QLQ-OG25)	To be completed by patient at Baseline Visit prior to start of treatment and at Visits 2, 3 & 4. Post original to OCTO* within **1 week** of patient completing.
PATIENT CONSENT FORM (TO BE KEPT AT SITE ONLY – DO NOT SEND TO OCTO)	To be completed by patient when consenting to participate in trial. Site staff to please complete a 'Patient Consent Notification Form' and post original to OCTO*.
PATIENT CONSENT NOTIFICATION FORM	Please complete once patient has completed Patient Consent Form and post original to OCTO* within 1 month.
PATIENT CONSENT WITHDRAWAL FORM (TO BE KEPT AT SITE ONLY – DO NOT SEND TO OCTO)	Please complete if patient withdraws from all aspects of the trial and does NOT wish to have their follow-up information included in the study. Site staff to please complete a 'Patient Consent Withdrawal Notification Form' and post original to OCTO*.
PATIENT CONSENT WITHDRAWAL NOTIFICATION FORM	Please complete once patient has completed Consent Withdrawal Form and post original to OCTO* within 1 month.
PREGNANCY NOTIFICATION FORM	Please complete upon awareness of pregnancy of trial patient or pregnancy of trial patient's partner, fax immediately to OCTO and post original to OCTO* within 1 month.
PROGRESSION AND DEATH FORM	Please complete in the event of Progression or Death, **Fax immediately** to Fax**: 0800 3891629** and post original to OCTO* within 1 month.
RANDOMISATION FORM	Please complete at randomisation and **Fax immediately** to Fax**: 0800 3891629**, post original to OCTO* within 1 month.
SAE FORM	Please complete when an SAE occurs and **Fax immediately** to Fax**: 0800 3891629**, post original to OCTO* within 1 month.

PATIENT SCREENING LOG	Please **Fax** to OCTO at the **end of each month** to Fax: 01865 617010, post original to OCTO* within 1 month of completion of trial.
PATIENT VISIT LOG	Please **Fax** to OCTO at the **end of each month** to Fax: 01865 617010, post original to OCTO* within 1 month of completion of trial.

*** Please post to the Oncology Clinical Trial Office (OCTO) using the FREEPOST address:**
FREEPOST RRTL-ALZY-CBRL
Oncology Clinical Trials Office (OCTO), COG Trial, Department of Clinical Pharmacology, University of Oxford, Old Road Campus Research Building, Old Road Campus, off Roosevelt Drive, Headington, Oxford, OX3 7DQ

APPENDIX 14. COG SUSAR REPORTING TO ASTRAZENECA

(FOR COG TRIAL OFFICE USE ONLY)

EXPEDITED SUSAR REPORTING:

COG Trial staff will report any Serious Unexpected Suspected Adverse Drug Reaction (SUSAR) that occurs during the study to AstraZeneca according to the following timelines:

- Any fatal and life-threatening SUSAR must be reported to AstraZeneca within one working day (from the point in time when COG trial staff become aware of it).

- All other SUSARs (i.e. non-fatal or non life-threatening) must be reported to AstraZeneca within five working days (from the point in time when COG trial staff become aware of them).

All other SAEs (i.e. reports of SAEs considered to be not study-drug-related and/or expected according to the investigator brochure), which do not qualify for expedited reporting, must be reported to AstraZeneca at least quarterly. A line listing may be used for this purpose.

All SUSARs and line listings should be faxed to AstraZeneca using the dedicated fax number.

FOLLOW UP:

Follow-up information on SUSARs must also be reported to AstraZeneca within the same timelines as above.

If the follow-up information on SUSARs makes the case fatal and/or life-threatening, this information must be sent to AstraZeneca within one working day, as above.

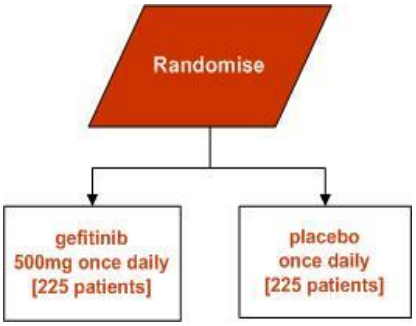
If a non-serious adverse event becomes a SUSAR, this and other relevant follow-up information must also be reported to AstraZeneca within the same timelines as above.

Please note that AstraZeneca will direct all queries to COG Trial staff only and not to the specific sites involved.

STUDY SUMMARY

Phase III, randomised, double-blind, placebo-controlled trial of gefitinib 500 mg once daily versus placebo in oesophageal cancer progressing after chemotherapy

Chief Investigator: Prof. David R. Ferry



STUDY OBJECTIVES	
Primary:	▪ To assess whether gefitinib will improve overall survival in patients with oesophageal cancer when compared to a placebo.
Secondary:	▪ To assess the toxicity of gefitinib monotherapy in oesophageal cancer patients. ▪ To assess whether gefitinib will have a significant positive or negative impact upon quality of life compared with placebo. ▪ To assess the impact gefitinib will have on progression-free survival compared with placebo. ▪ To identify if there are genetic signatures associated with benefit. (this will be done in a translational research project [HANDEL] as a separate protocol).

STUDY DESIGN	Phase III randomised, multi-centre, double-blind, placebo-controlled
STUDY POPULATION	450 patients
INCLUSION CRITERIA	1. Age ≥18 years 2. Oesophageal cancers and type I and type II junctional tumours 3. Histologically proven adenocarcinoma, squamous cell cancer or poorly differentiated epithelial malignancy 4. Failure after previous chemotherapy. Treatment not to start until at least 6 weeks from the last day of chemotherapy (including oral) 5. WHO Performance Status 0, 1 or 2 6. Measurable or evaluable disease by CT scan 7. Able to take tablets (whole or dispersed) 8. Patients with brain metastases must be stable and have received cranial irradiation prior to entry
EXCLUSION CRITERIA	1. More than 2 previous chemotherapy regimens and one chemoradiation course. 2. Presence of previous or other malignancy likely to confound results or interfere with gefitinib therapy 3. Medical condition considered to interfere with the safe participation in the trial 4. Radiotherapy to site of measurable or evaluable disease in the last 4 weeks 5. Pregnancy 6. Sexually active patients of child-bearing potential not using adequate contraception (male and female) [post menopausal women must have been amenorrheic for at least 12 months to be considered as having non-child-bearing potential] 7. Serum bilirubin greater than 3 times the upper limit of reference range (ULRR) 8. Aspartate aminotransferase (AST/SGOT) or alanine aminotransferase (ALT/SGPT) ≥ 2.5 x ULN if no demonstrable liver metastases (or >5 x in presence of liver metastases) 9. Any evidence of clinically active Interstitial Lung Disease (ILD) (patients with chronic, stable, radiographic changes who are asymptomatic need **not** be excluded) 10. Known severe hypersensitivity to gefitinib or any of the excipients of this product 11. On cytotoxic chemotherapy, immunotherapy, hormonal therapy (excluding contraceptives and replacement steroids) or experimental medications

Necessary Additional Data

Click here to download Necessary Additional Data: Panel for Lancet Oncology_v1.0_14Apr2014.docx

Necessary Additional Data

Click here to download Necessary Additional Data: COG Analysis v2.0_30Mar2012-signed.pdf

Date: 21/11/2013
To: "David R Ferry" profdavidferry@gmail.com
From: "The Lancet Peer Review Team" eesTheLancet@lancet.com
Subject: Your submission to The Lancet
Manuscript reference number: THELANCET-D-13-07934
Title: Gefitinib for oesophageal cancer progressing after chemotherapy: a multicenter double-blind, placebo-controlled randomised control trial (COG)

Dear Prof Ferry,

Many thanks for submitting your manuscript to The Lancet. Following external peer review, several editors here have discussed the manuscript, but their decision was that it would be better placed elsewhere.

The reviewers' comments and some editorial points that may be of interest to you are presented in the paragraphs below. I hope you find these comments helpful.

Yours sincerely,

Dr Astrid #James
The Lancet

Reviewer #1: My comments are below.

1. How was the proportionality of hazards (PH) assumption verified? Show the results for this. The PH assumption is robust, but it can break down for treatment, especially in an RCT.

2. What I expect to see in a resubmission are references to the statistical literature. Your results depend on correct application of methods, coupled with a knowledge of the literature. Some authors for you to chase up are given below.

3. Hazard ratios, while useful, are not the only metric that comes from Cox modelling. Harrell has written around this subject area.

4. An issue with model building is overfitting. How was this addressed? Peduzzi and colleagues have written about this for survival data.

5. Your first survival curve should be over all patients irrespective of treatment group. Include on this figure a 95% CI (CIs not necessary when you compare the treatment groups). Do the basics first. You don't need to include hazard ratios on survival curves. Survival curves show visually a picture of what is going on. Stuart Pocock (Lancet, 2003) wrote a nice paper telling readers how to present them. Make more of an effort to tell the reader how to interpret. For example, what do the long flat lines at the end mean for your data?

6. I may have missed this, but what was the censoring date?

7. You jump into calculating hazard ratios before doing the basics. Document carefully the

distribution of the primary outcome measure (deaths) by some of the demographic and clinical characteristics outlined in Table 1.

8. Analysis of covariance to be written in full when first met. What assumptions underpin it, and how were they verified? What remedial action was undertaken if an assumption broke down? There is no logic in adjusting these analyses for baseline covariates given this is an RCT (key here lies in understanding the design). Either Bland or Altman or both have written about this.

9. How was missing data accommodated in the statistical modelling?

10. It's unnecessary to compare adverse events and post-treatments statistically. These are not powered outcomes (even if significant). A simple list of these will go a long way.

11. Reference the power calculation.

12. I don't like the term 'reaching significance' (abstract). Statistical significance is not an outcome measure, and is arbitrarily set by the researcher. The abstract results' section should focus on the primary outcome measure.

13. Table 1. Drop mean/SD for age leaving median (25th/75th centiles). Report percentage to nearest whole number. BMI units.

14. The discussion is biased in favour of the (significant) secondary outcomes. A non-significant difference between treatments for all-cause mortality is worth reporting, and should be the focus.

Reviewer #3: This was a large placebo-controlled phase III randomised trial designed primarily to detect possible benefits in overall survival among patients given the drug gefitinib orally as second as second line chemotherapy ("palliative chemotherapy") in oesophageal cancer patients. Secondary outcomes were progression free survival and selected patient reported outcomes (global quality of life, dysphagia, difficulty eating and odynophagia) at 4 weeks after randomisation. This was a well-designed study of an interesting and clinically relevant topic, but the conclusions drawn do not match the findings.

Major comments:
1. The text gives a general sloppy impression. Abbreviations are for example used without explanations. British spelling is preferred for Lancet, e.g. oesophagus instead of esophagus.
2. The Introduction section would benefit from a clearer focus on the subject addressed in the present study. The aims of the study are e.g. not clearly defined, since the indication for treatment is e.g. not clearly stated.
3. "Progression free survival" is very difficult to assess accurately and should therefore be given little attention compared to the main outcome and patient reported outcomes.
4. The substantial level of toxicity associated with the test drug is ignored in the Discussion section and the Conclusion.
5. Patient reported outcomes data were unfortunately not reported in any table, but there seem to be no clinically relevant differences between the treatment groups. A table presenting these

results is suggested. My opinion is that patient reported outcomes are most important in studies evaluating palliative therapy, probably more important than a few extra days of possibly longer survival.
6. The conclusion of recommending patients with progressive oesophageal cancer gefitinib does not seem justified based on the results of this trial. The study did not show any survival benefit (main outcome) and no clear benefits from a patient reported outcome point of view. The toxicity should not be ignored as an important issue for these patients. I would rather suggest the conclusion that the trial shows no reason to recommend gefitinib as a palliative chemotherapy in this group of patients.

Minor comments:
1. This is a multi-centre trial, which should be stated in the methods section.
2. I suggest the authors to present survival data in days rather than using two decimals of months, which makes it difficult to understand the level of absolute difference.

Reviewer #4: This is a well-designed and well-conducted trial. The paper is clearly written and follows the CONSORT guidelines. The trial is negative on the primary outcome (overall survival) with no overall survival benefit for the experimental arm. Outcomes in the control arm are those usually reported.
Major points
- The primary outcome chosen is the one to be chosen for such disaster pathology. The second outcome of importance in metastatic oesophageal cancer is HRQL. In the protocol, authors specified that they will consider HRQL as a secondary outcome with pre-specified analyses for global HRQL, dysphagia, eating and pain and that other HRQL variables will be examined exploratively. All the pre-defined HRQL measures are not statistically different between the treatment and the control groups. Authors assessed that odynophagia reached clinical and statistical significance (p=0.004), however it is not per se a predefined HRQL outcome. Other HRQL results reported, even if positive, are exploratory (social functioning, constipation, cough, speech)
- Since gefitinib administration was associated more frequently with diarrhea, I'm not sure that the HRQL constipation domain is relevant.
- PFS has been introduced as a secondary outcome. A statistical difference of 0.4 months was found favoring the experimental arm with a p value of 0.020. This difference of 11 days favoring the experimental arm is definitely not clinically relevant, especially if considering associated adverse events and product cost. This should be clearly underlined and discussed by the authors.
- In relation with the previous comment I'm not agree with the way chosen by the authors to present their result. Figure 3B is not relevant since based on PFS. This lead to some confusion. Subgroup analyses should be given on the primary outcome, ie OS. In the same way, the second paragraph of the discussion highlights that the trial is positive for PFS with discussion of subgroups that might benefit from the experimental treatment. Even if statistically positive, the results found are not medically relevant (see above). This paragraph of the discussion section should be dedicated to the primary outcome, not to a secondary outcome.
- Since the vast majority of patients did not receive any additional line of chemo thereafter, how the authors explain that PFS benefit did not translate into OS benefit?
- It is not clear if patients having recurrent disease within the radiotherapy field would be

eligible to the study. It is expected that chemo or targeted therapy may be inefficient in such conditions. Exploratory analysis would be of interest to be provided, and if the numbers concerned are high this may have negatively impact on the study results. To be also discussed.

- Not agree with the authors' explanation that no stratification has been done as prognostic factors have not been identified in this patient population. Performance status (predominantly) and histological subtype (with lower evidence) are usually used. PS is confirmed a posteriori by the authors as a strong prognostic factor in the present study. For histological subtype, there is no phase III randomized trial giving evidence for any benefit of palliative chemo in oesophageal SCC whereas some evidence exists for adenocarcinoma (frequently mixed with junctional and gastric locations).
- On an ethical point of view I'm not convinced by conducting a large phase III randomised trial with phase II studies having provided a response rate of only 9% in unselected populations.
- In the discussion section we would expect some arguments to explain such negative results more than trying to focus on the statistical significance in some subgroups.

Minor points

References should be presented in THE LANCET dedicated format.

Reviewer #5: Major comments

1. In general, efficacy of molecular targeted therapy for metastatic disease is assessed by disease-control rate, response rate, progression-free survival, and overall survival. Among them, response rate is not delineated in the abstract and the text.
2. In the Discussion, the sentence "these phase II trials did not select patients on the basis of predictive biomarkers, because none are known for gefatinib in oesophageal cancer" may not be correct. Female gender and EGFR expression may be associated with better outcomes in the treatment of advanced oesophageal cancer with gefatinib (Janmaat ML, Gallegos-Ruiz MI, Rodriguez JA, et al: Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients. J Clin Oncol 24:1612-1619, 2006).

Minor comments

In the Introduction, referring to a study by Wang KL and colleagues, "EGFR receptors are expressed in the majority of oesophageal cancers" may mislead the readers to the conception that all oesophageal cancers are potentially candidates for targeted therapy with EGFR antagonists. In a study by Wang and colleagues, EGFR was expressed in 33 of 103 adenocarcinomas (32%).