A Phase II Study of Gefitinib Monotherapy in Advanced Esophageal Adenocarcinoma: Evidence of Gene Expression, Cellular, and Clinical Response

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Abstract

Purpose: At presentation, most cases of adenocarcinoma of the esophagus (ACE) are inoperable. Although chemotherapy can prolong survival, patients eventually die as a result of refractory disease. Epidermal growth factor receptor (EGFR) is almost universally expressed in ACE and is a negative prognostic factor.

Experimental Design: This open-label, two-center, noncomparative, two-part phase II trial assessed the EGFR tyrosine kinase inhibitor gefitinib (500 mg/d) in patients with advanced, inoperable ACE. The primary end point was tumor response. The effect of EGFR inhibition was also evaluated by gene expression analysis of tumor biopsies taken before gefitinib treatment and 28 days after.

Results: Twenty-seven patients were recruited and evaluable for tumor response and safety. Three patients had a partial response and seven had stable disease, giving a disease control rate (partial response + stable disease) of 37%. Drug-related adverse events were generally mild: diarrhea in 19 (grade 3 in three) and rash in 19 (grade 3 in five) patients, and there were no grade 4 drug-related adverse events. Microarray experiments on tumor biopsies showed that gefitinib also down-regulated oncogenes associated with tumor progression. Ki67 (a marker of tumor growth) expression decreased in five of seven biopsies taken before and after treatment.

Conclusion: Gefitinib (500 mg/d) is an active and generally well-tolerated treatment for ACE. Studies on endoscopic biopsies are feasible and indicate that gefitinib inhibits both gene expression and cellular biology at 500 mg/d, and these may provide surrogate end points for predictive biomarkers. Further trials of gefitinib are warranted, particularly as patient response seems to be durable and current second-line chemotherapy options have no proven ability to prolong life.

The incidence of adenocarcinoma of the esophagus (ACE) has increased 3-fold over the past two decades, from 5/100,000 to 15/100,000 (1). At diagnosis, 80% of cases are inoperable (2) and, of those with early local disease who have surgery as part of their treatment, only 15% to 30% will be cured (3–5).

Chemotherapy provides some clinical benefit for the majority of patients with advanced disease, with response rates of 45% and median survival of 10 months (5, 6). For patients previously treated with chemotherapy, there is no standard systemic treatment option with a proven survival or palliative benefit shown in randomized trials.

ACE is associated with one of the most common premalignant lesions, Barrett’s metaplasia. This provides a focus for early detection and intervention. The epidermal growth factor receptor (EGFR) is frequently expressed in ACE, and activation of the EGFR signaling pathway has been implicated in the progression of Barrett’s metaplasia to ACE (7). Tumor necrosis factor-α is also up-regulated in Barrett’s metaplasia (8) and further increases EGFR expression. It has been suggested that EGFR expression might have prognostic value for patients with Barrett’s-associated adenocarcinoma, particularly those with stage II cancer (9). EGFR expression has also been associated with a poor response to therapy, development of cytotoxic drug resistance, disease progression, and poor survival (10–13). Hence, an emerging understanding of the molecular events that characterize the transition to carcinoma may provide novel targets in cancer therapy such as EGFR and tumor necrosis factor-α.

Gefitinib (Iressa) is the first in a new class of anticancer agents (EGFR tyrosine kinase inhibitors). In pretreated patients with advanced non–small cell lung cancer, gefitinib administered at 250 mg/d has shown antitumor activity, disease stabilization, and rapid symptom improvement (14, 15).
We aimed to address the efficacy and safety of gefitinib (500 mg/d) in patients with inoperable ACE and to assess the biological effects of EGFR inhibition using *ex vivo* immunohistochemistry studies, Western blot analysis, DNA sequencing, and microarray technology.

**Patients and Methods**

**Trial design.** This open-label, two-center, noncomparative, two-part phase II trial recruited patients with advanced, inoperable ACE. The primary objectives were to assess the tumor response rate for oral gefitinib (500 mg/d). The secondary objectives were to estimate progression-free survival, duration of response, and disease control rate (response plus stable disease); to evaluate changes in quality of life (QoL); and to assess safety by evaluation of adverse event (AE) and serious AE data. Exploratory investigation included the assessment of the inhibition of EGFR phosphorylation and effects on downstream signaling pathways.

After treatment for 1 month, only patients with objective radiologic response, stable disease, or clear palliative benefit continued therapy until disease progression (Fig. 1). Eighteen patients were to be enrolled in the first phase of the study. If there was at least one response in these 18 patients, an additional 9 patients were to be enrolled.

**Patient eligibility.** All patients provided written, informed consent. ACE was classified according to the WHO classification of esophageal tumors (16). Barrett’s esophagus was also confirmed histologically, in association with endoscopic findings using accepted criteria (17–19).

Inclusion criteria were histologically confirmed ACE or adenocarcinoma of the esophagogastric junction, locally advanced or metastatic disease that was incurable with surgery, measurable disease according to Response Evaluation Criteria In Solid Tumors standards, the ability to swallow tablets (patients with dysphagia could have dilation or metal stent insertion prior to trial entry), and those aged ≥18 years.

Patient exclusion criteria included previous treatment with more than one chemotherapy regimen, first-line chemotherapy within the past 2 months, radiotherapy to the esophagus or mediastinum in the past 2 months, other coexisting malignancies or malignancies diagnosed within the past 5 years, with the exception of basal cell carcinoma or cervical cancer *in situ*, any unresolved chronic toxicity greater than grade 2 (National Cancer Institute Common Toxicity Criteria) from previous anticancer therapy, any evidence of severe or uncontrolled systemic disease (in the opinion of the investigator), pregnancy or breast-feeding, and any evidence of clinically active interstitial lung disease.

**Safety and tolerability.** All AEs were reported and their severity assessed using National Cancer Institute Common Toxicity Criteria version 2.0. Dose interruptions were used as the first approach in managing toxicity. Repeat dose interruptions were allowed, as required, for ≤14 days on each occasion. Only one dose reduction per patient was permitted, from 500 to 250 mg/d.

**Efficacy.** Tumor response assessments were done during screening and every 28 days after the start of treatment until disease progression using Response Evaluation Criteria in Solid Tumors and computed tomography (CT) scans or X-rays. Responders were defined as patients satisfying Response Evaluation Criteria in Solid Tumors for complete response or partial response and stable disease, and were present for at least 8 weeks. Best responses were assigned on withdrawal or 6 months after the first dose of gefitinib. Duration of response was defined as the interval between the date of first documented response and the date of objective, documented disease progression.

**Disease control and progression-free survival.** Disease control rate was defined as patients with complete response/partial response plus patients with stable disease confirmed and sustained for ≥4 weeks. Time to progression was assessed for each patient and defined as the number of days from the first day of treatment to either death or progression, or the last date of patient contact.

**QoL assessment.** The effect of ACE on symptoms, in particular dysphagia, was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire QLQ-C30 and the esophageal cancer–specific module QLQ-OES 24, which uses a four-point scale (the lower the value, the less severe the effect). Questionnaires collected at baseline and after 1 and 2 months of treatment were analyzed statistically using a Wilcoxon signed-rank test.

**Biomarker analysis.** Esophageal tumor and surrounding metastatic tissue biopsies were taken at baseline and on day 28. Samples were made anonymous according to Medical Research Council Good Clinical Research Practice guidelines and were collected using local National Health Service Ethical Committee guidelines.

Biopsies were analyzed for EGFR, phosphorylated (p-)EGFR, Ki67, ERK, p-ERK, Akt, p-Akt, β-catenin, and γ-catenin by immunohistochemistry using the following primary antibodies: EGFR, p-EGFR, β-catenin, and γ-catenin (Santa Cruz Biotechnology), Ki67 (Transduction Laboratories), ERK1/2 (p44/42 mitogen-activated protein kinase antibody), and p-ERK1/2, Akt1, and p-Akt1 (Cell Signaling Technology). Western blot analysis (20) was also carried out using the following antibodies: EGFR, p-EGFR, E-cadherin (Santa Cruz Biotechnology), β-catenin, p-ERK, and p-Akt (Sigma-Aldrich).

**Microarray analysis.** Microarray analysis on paired biopsy samples was done independently by Cancer Research U.K. (21). Spot signal measurements used in the analysis were median spot signal values corrected for subtraction of local median background from each spot. Spot signals were excluded from the analysis if they were not significantly different from the background in both channels (using a Mann-Whitney test at 0.001 significance level) or by visual inspection. Differential gene selection was done by selecting genes that showed a fold change of 2-fold or greater in the same direction of change across all samples. Genes with significant fold changes, but with low measurement precision, were rejected from the list using the GeneSpring Global Error Model. Candidate genes were ranked according to the geometric mean of their fold change.

**Statistical analysis.** The Cancer Research U.K. and AstraZeneca Oncology Trials Group provided statistical advice for all aspects of this study. To assess whether parametric and nonparametric data should be used, data were examined for distribution with ANOVA/t tests and Mann-Whitney *U* tests, respectively. Survival curves were calculated using modified Kaplan-Meier tests.

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![Fig. 1. Trial design.](image-url)
Results

Patients. A total of 27 patients were enrolled in the study and treated with gefitinib (500 mg/d; Table 1). The first patient was recruited on March 13, 2002 and the last patient was recruited on July 8, 2003. The majority of patients were male (85%), had a WHO performance status of 0 (63%), and all patients had measurable disease. All 27 patients were analyzed for efficacy and safety.

Safety and tolerability. Most AEs were mild (National Cancer Institute Common Toxicity Criteria grade 1 or 2). Twenty-five patients (92.6%) experienced drug-related AEs, with the most common being diarrhea, rash, and dry skin (Table 2). Eight patients experienced grade 3 drug-related AEs which, as previously reported for gefitinib, were diarrhea and skin rash. There were no grade 4 drug-related AEs.

The median (range) overall exposure to gefitinib was 68 (8-336) days. Three patients had a dose reduction to 250 mg/d for a median duration of 23 days; this was due to drug-related toxicity for two patients (grade 2 diarrhea and grade 3 rash, respectively), whereas the other patient reduced his dose without consultation. One patient discontinued treatment due to a grade 3 drug-related rash.

Disease control and survival. Median progression-free survival was 1.9 months (95% confidence interval, 1.0-2.7; Fig. 2A). Five patients (18.5%) were progression-free at 6 months. Median overall survival was 4.5 months (Fig. 2B). Fifteen patients had disease progression and two were not evaluable because they were too ill to attend CT scanning. There were no grade 4 AEs in patients (n = 27).

Patient X was a 51-year-old woman who received epirubicin, cisplatin, and 5-fluorouracil (5-FU) chemotherapy for stage IV adenocarcinoma of the distal esophagus, achieving a partial response. When she developed dysphagia, a CT scan revealed local, hepatic, and pulmonary disease. This patient rapidly achieved dysphagia palliation and on day 28 of treatment with gefitinib (500 mg/d), there was improvement in all disease sites. She had grade 3 skin toxicity that improved without treatment interruption or dose reduction.

Patient Y, a 52-year-old woman who was wheelchair-bound due to arthritis, was found to have an adenocarcinoma from 35 to 40 cm aboral (or from the incisors) in the distal esophagus (Fig. 3A) with pulmonary metastases. She was deemed unfit for chemotherapy. A metal stent had provided only minimal relief of her dysphagia. By day 28 of treatment with gefitinib (500 mg/d), her swallowing was much improved and she could manage solid food; concomitantly, a CT scan showed improvement of her primary tumor and pulmonary disease (Fig. 3B).

Patient Z was a 46-year-old woman who had received epirubicin, cisplatin, and 5-fluorouracil (5-FU) chemotherapy for stage IV adenocarcinoma of the distal esophagus, achieving a partial response. When her disease progressed 41 weeks later, the mass had been reduced to a 2 to 3 cm abnormality. When her disease progressed 41 weeks later, the mass had been reduced to a 2×3 cm abnormality. When her disease progressed 41 weeks later, the mass had been reduced to a 2×3 cm abnormality. When her disease progressed 41 weeks later, the mass had been reduced to a 2×3 cm abnormality. When her disease progressed 41 weeks later, the mass had been reduced to a 2×3 cm abnormality.

<table>
<thead>
<tr>
<th>Table 1. Patient demography</th>
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<tr>
<td>Patients, n</td>
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<tr>
<td>Sex, n (%)</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Mean age (SD), y</td>
</tr>
<tr>
<td>WHO performance status, n (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>Mean time from diagnosis to start of treatment (SD), mo</td>
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<tr>
<td>Measurable tumors and metastases, n (%)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Primary</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Lung</td>
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<tr>
<td>Local lymph nodes</td>
</tr>
<tr>
<td>Distant lymph nodes</td>
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<tr>
<td>Skin/soft tissue</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Prior therapy, n (%)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Chemotherapy</td>
</tr>
<tr>
<td>Surgery</td>
</tr>
<tr>
<td>Radiotherapy</td>
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<tr>
<td>No prior chemotherapy&lt;sup&gt;‡&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note: Intent-to-treat population.

<sup>*</sup>Patients could have more than one site of metastasis.

<sup>†</sup>Patients could have received more than one type of therapy.

<sup>‡</sup>Seventeen patients had epirubicin, cisplatin, and 5-FU therapy; one had cisplatin/5-FU therapy.

<sup>§</sup>Patients who had declined chemotherapy or were too frail to receive it.

Table 2. Drug-related grade 1/2 AEs occurring in ≥5% of patients plus all drug-related grade 3 AEs in patients (n = 27) treated with gefitinib (500 mg/d)

<table>
<thead>
<tr>
<th>AE</th>
<th>Grades 1/2</th>
<th>Grade 3&lt;sup&gt;*&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>16 (59.3)</td>
<td>3 (11.1)</td>
</tr>
<tr>
<td>Rash&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (51.9)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10 (37.0)</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>3 (11.1)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (7.4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Intent-to-treat population (n = 27).

<sup>†</sup>No grade 4 AEs reported.

<sup>‡</sup>Includes macular, papular, pustular, general, and not otherwise specified rash.
QoL. For overall health and QoL (EORTC QLQ-C30), there was minimal or no change from baseline. However, a significant improvement in constipation at 1 and 2 months ($P = 0.02$ and $P = 0.03$, respectively) and a significant worsening of diarrhea at 1 month ($P = 0.01$) were reported. There were no significant changes from baseline in any of the EORTC QLQ-OES 24 scores, which assessed symptoms with particular reference to dysphagia.

**Biomarker analysis.** In a hypothesis-generating analysis, paired tumor biopsies before and after gefitinib administration were available for seven patients. Following gefitinib treatment, a significant reduction in Ki67 levels ($P < 0.05$) was observed in five of the seven patients (Fig. 4). Proven EGFR mutations were observed in two esophageal adenocarcinomas, one missense L858R, and one in-frame deletion delE746-A750 (previously reported in ref. 34). There was also no significant difference observed for EGFR, p-EGFR, ERK, p-ERK, Akt, p-Akt, $\beta$-catenin, or $\gamma$-catenin expression using immunohistochemistry or Western blot analysis, either before or after gefitinib treatment or between responders and nonresponders. The change in p-EGFR levels, although not statistically different, do indicate that in five individual patients there was suppression of p-EGFR expression after therapy (one case had a marked suppression of p-EGFR expression following a clinical response; Fig. 5). It is difficult to know how much this relates to the fact that we had only seven paired biopsies.

**Microarray analysis.** Out of 12 paired slides that were visually inspected for microarray analysis, 2 slides were used for initial gene selection and another 2 slides were used to support the initial gene selection. A scatter plot of a microarray result set from one patient is presented in Fig. 6. Twenty genes showed statistically significant alterations in expression following treatment with gefitinib (Table 4). Interestingly, of the genes that were down-regulated following treatment of

![Fig. 2. Kaplan-Meier graph showing (A) progression-free survival and (B) overall survival among 27 patients with ACE treated with gefitinib (500 mg/d). Censored observations (ticks).](image)

![Fig. 3. CT scans of patient X (A) at baseline and (B) after 4 wk of gefitinib (500 mg/d); patient Y (C) at baseline and (D) after 4 wk of gefitinib; and patient Z (E) at baseline and (F) after 8 wk of gefitinib.](image)

<table>
<thead>
<tr>
<th>Table 3. Best tumor response to gefitinib (500 mg/d)</th>
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<tbody>
<tr>
<td>Patients, $n$ (%)</td>
</tr>
<tr>
<td>Partial response</td>
</tr>
<tr>
<td>Stable disease</td>
</tr>
<tr>
<td>Progressive disease</td>
</tr>
<tr>
<td>Not evaluable</td>
</tr>
</tbody>
</table>

NOTE: Intent-to-treat population ($n = 27$).
gefitinib, five were oncogenes: LCN2, which is associated with HER2-positive breast cancer (22); JAG1, which enhances angiogenesis in response to growth factors (23); LTBR, a tumor necrosis factor C receptor (24); MNAT1, which activates and stabilizes cyclin-dependent kinases (25); and Akt1, which activates several signaling cascades such as phosphoinositide-3-kinase (26). CASP8, an upstream protease of the apoptosis cascade, was also down-regulated (27).

Discussion

This open-label, noncomparative, phase II trial evaluated the efficacy and safety of gefitinib (500 mg/d) in patients with advanced, inoperable ACE. Results indicated that gefitinib might be beneficial for some patients who have exhausted one or more standard treatment options for ACE, including those who are unsuitable for chemotherapy. Among the 27 patients treated, the response rate was 11% and the disease control rate was 37%, with median progression-free survival of 1.9 months. A disease control rate of 37% is impressive, given that this patient population is extremely difficult to treat.

Although patients able to tolerate cisplatin-based chemotherapy (principally epirubicin/cisplatin/5-FU in Europe and cisplatin/5-FU in the U.S.) have improved survival and often good dysphagia palliation, they have no second-line options proven to prolong life or improve QoL. This is in marked contrast to many other disease sites for which second-line therapy with significant clinical benefit has emerged in the past decade, not least in non–small cell lung cancer. Only a small number of published data are available on the role of second-line chemotherapy. In a phase II trial of weekly irinotecan plus docetaxel of 24 patients (28), the overall response rate was...

![Fig. 4. Paired tumor Ki67 levels before and after gefitinib therapy, analyzed by immunohistochemistry. * P < 0.05 versus pretherapy levels.](image1)

![Fig. 5. Changes in Phos-EGFR pre- and 4 wk post-gefitinib. There is no statistical difference but a trend exists, perhaps suggesting Iressa blockade of Phos-EGFR.](image2)

![Fig. 6. Scatter plot of microarray results from one patient. Background-corrected normalized signal measurements from the Cy5 channel against measurements from the Cy3 channel for a single chip. Each measurement used was calculated from the median spot signal intensity by subtracting local median background. The measurements from this sample were used in the final data analysis.](image3)

![Table 4. Increases (>2.0) and decreases (<0.5) in gene expression following exposure to gefitinib (500 mg/d).](table1)
12.5%. In another phase II study of 38 patients using irinotecan and 5-FU/leucovorin, the overall response rate was 29% (29). Despite the activity reported in these two studies, toxicity was considerable and many patients were unable to tolerate these treatment regimens.

With respect to safety, gefitinib (500 mg/d) was well tolerated in this study; few patients required dose reductions or withdrawal from therapy. Drug-related AEs were common but generally mild (grade 1/2), consisting mainly of diarrhea and skin reactions.

Two other phase II trials, one using gefitinib (30), and the other, the oral EGFR inhibitor erlotinib (31), have been published. The gefitinib trial included nine patients with squamous cell cancer. To their credit, these authors planned to biopsy their study patients four times a week during the trials, resulting in 24 patients being evaluable for EGFR expression, 13 for pAKT and 22 for pERK. No biological correlates with response or survival were found. In the trial using erlotinib, 43 patients with gastroesophageal junction tumors were studied along with 25 patients with gastric cancers. Their response rate of 9% in the gastroesophageal junction group is similar to what we report here. In contrast with our trial and that of Jannmaat et al. (30), this trial used historical archive specimens for the assessment of biological correlates, EGFR expression, pAKT, and transforming growth factor-α were assessed but did not correlate with clinical outcomes. These authors also measured serum epithelial growth factor levels and did a proteomic analysis of plasma which did not provide informative results.

A more extensive pharmacodynamic study in gastric (80%) and gastroesophageal junction cancer (20%) is reported in biopsies from 35 patients who had, as in our study, a pretreatment sample and a day 28 sample (32, 33). It is not clear how many patients with gastroesophageal junction cancers were assessed because the data from the two tumor sites were pooled, but the global result was that there was a correlation, which was proportionate and linear, between apoptotic index and gefitinib AUC0-24 and Cmax. This result is of importance and indicates that it may be important to use higher doses of gefitinib in esophageal cancer.

The phase II trials of gefitinib and erlotinib in esophageal cancer have a consistency in outcome, all report an ~10% response rate, but the approach to assessing biological effects varied. The biological effect we report, which is novel, is the use of gene expression technology. We intend to develop a technology platform to allow the evaluation of gene expression analysis in a planned placebo-controlled phase III trial in this disease.

Tumor biomarker expression and microarray analysis showed that gefitinib modulated the expression of multiple genes. Applying a reasonably stringent analysis, oncopgenes associated with tumor progression were down-regulated, and the down-regulation of CASP8, which increases apoptosis, might be a mechanism of gefitinib or prior chemotherapy resistance. Although we have not done terminal nucleotidyl transferase-mediated nick end labeling assays in this study, we did undertake the evaluation of caspase-3 expression with immunohistochemistry. There was no clear difference before and after gefitinib but small phase II trials could conceivably have missed a subgroup in which there was an effect. However, our microarray data gives a lead, in that overall, there was a net decrease in caspase-8. Clearly, data from hundreds of paired samples will be needed to define the gefitinib-induced changes that relate to response, stable disease, and longer survival.

Reductions were, however, observed in the expression levels of Ki67 after treatment with gefitinib. These data are important because they indicate that a potential biomarker of either target validation or therapy response might be one of the most straightforward to determine through cell proliferation immunohistochemistry of routine hospital specimens. However, target validation in large randomized placebo-controlled trials with blockade of EGFR pathways might provide this information. We have shown previously that EGFR mutations do not correlate with response (34).

In a patient population for which current chemotherapy second-line treatment options are often toxic, further trials of gefitinib would seem to be warranted, particularly in patients who either cannot or do not wish to tolerate the toxicities associated with chemotherapy, including the neoadjuvant and long-term adjuvant settings. The inclusion of microarray analysis will allow this new technology to be evaluated prospectively, and in the United Kingdom, a randomized trial of gefitinib versus placebo will be undertaken to attempt to define whether there is a subgroup of patients more likely to benefit.

Acknowledgments

AstraZeneca for providing gefitinib, Rachel Edwards (AstraZeneca, Luton, United Kingdom) and Lea-Anne Harrison (University Hospitals of Leicester NHS Trust, Leicester, United Kingdom) for providing technical support, colleagues in New Cross Hospital (Wolverhampton, United Kingdom) for assisting with data collection and CTS.cans, Dr. Tim Gant (Medical Research Council Centre, Leiceste, United Kingdom) for assisting with array chips, and Mark Walker from Complete Medical Communications, who provided medical writing support on behalf of AstraZeneca.

References

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