Matuzumab plus epirubicin, cisplatin and capecitabine (ECX) compared with epirubicin, cisplatin and capecitabine alone as first-line treatment in patients with advanced oesophago-gastric cancer: a randomised, multicentre open-label phase II study

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Background: Clinical data showed promising antitumour activity with feasible tolerability for matuzumab plus epirubicin, cisplatin and capecitabine (ECX) chemotherapy in untreated advanced oesophago-gastric (OG) cancer. The aim was to evaluate the efficacy of matuzumab plus ECX versus ECX alone.

Patients and methods: In this multicentre, randomised open-label phase II study, 72 patients with metastatic OG cancer were randomly assigned to either 800 mg matuzumab weekly plus epirubicin 50 mg/m2, cisplatin 60 mg/m2 on day 1 and capecitabine 1250 mg/m2 daily in a 21-day cycle (ECX) or the same ECX regimen alone. The primary end point was objective response. Secondary end points included progression-free survival (PFS), overall survival (OS), quality of life, safety and tolerability.

Results: Following random assignment, 35 patients (median age 59 years) received ECX/matuzumab and 36 patients (median age 64 years) ECX. The addition of matuzumab to ECX did not improve objective response: 31% for ECX/matuzumab [95% confidence interval (CI) 17–49] compared with 58% for the ECX arm (95% CI 41–74) \( P = 0.994 \) (one sided). There was no significant difference in median PFS: 4.8 months (95% CI 2.9–8.1) for ECX/matuzumab versus 7.1 months (95% CI 4.4–8.5) for ECX, or in median OS: 9.4 months (95% CI 7.5–16.2), compared with 12.2 months (95% CI 9.8–13.8 months). Grade 3/4 treatment-related toxicity was observed in 27 and 25 patients in the ECX/matuzumab and ECX groups, respectively.

Conclusion: Matuzumab 800 mg weekly combined with ECX chemotherapy does not increase response or survival for patients with advanced OG cancer. Therefore, ECX/matuzumab should not be examined further in phase III trials.

Key words: advanced, anti-EGFR, chemotherapy, oesophago-gastric cancer, randomised, treatment

Introduction

Oesophageal and gastric cancer remain a significant health burden and are the second and sixth most common causes of cancer deaths globally [1]. For advanced disease, combination chemotherapy has demonstrated a survival benefit compared with best supportive care [2, 3]. There is no universally accepted standard regimen for chemotherapy-naive advanced oesophageo-gastric (OG) cancer. At the time of designing this study, epirubicin, cisplatin and 5-fluorouracil (5FU) (ECF) was a reference regimen in Europe on the basis of two phase III studies and a meta-analysis [4–6]. Furthermore, the interim results from the phase III REAL-2 study [a four-arm study evaluating the substitution of capecitabine for 5FU and oxaliplatin for cisplatin: ECF, EOF, ECX and EOX (E, epirubicin; C, cisplatin; F, 5FU; O, oxaliplatin)] had demonstrated acceptable safety profile and encouraging antitumour activity for capecitabine 1250 mg/m2 daily combined with epirubicin and cisplatin (ECX) [7]. The substitution of capecitabine for continuously infused 5FU obviates the need for central venous catheters and their associated complications and is preferable for patients provided efficacy is not compromised [8–10]. Recently, the
patients and methods

Patients

Patients with histopathologically confirmed metastatic gastric adenocarcinoma or adenocarcinoma of the lower third of the oesophagus who had not received prior chemotherapy for advanced disease underwent screening for intratumoral EGFR expression after initial written informed consent. Only patients with EGFR-positive tumours were enrolled into the study.

Other eligibility requirements included radiologically measurable disease, Eastern Cooperative Oncology Group (ECOG) performance status 0/1, minimum age of 18 years, normal cardiac function (left ventricular ejection fraction within the institutional normal range), a minimum 12-month interval from completion of any neoadjuvant or adjuvant chemotherapy, a minimum 4-week interval from completion of radiotherapy and adequate liver, bone marrow and renal function as defined by alanine aminotransferase/aspartate aminotransferase no greater than 5× the upper limit of normal (ULN), bilirubin <1.5× the ULN, neutrophils >1500 mm³, platelets >100 000/μl, haemoglobin >10 g/dl and serum creatinine <1.5× the ULN or glomerular filtration rate (GFR) of 260 ml/min. Before any treatment, all patients provided a second written informed consent and the treatment protocol was approved by all relevant local ethics committees.

Tumour material was obtained from the initial tumour resection or diagnostic biopsy. EGFR expression was evaluated by a central pathologist in representative paraffin-embedded tumour blocks using the EGFR pharmDx test kit from DakoCytomation. Tumours were considered positive if any membrane staining above background level was observed.

Randomisation was carried out centrally in a blinded manner by telephone using an interactive voice response system with the random sequence previously generated by a computer programme in a 1 : 1 ratio and involved stratification for the site of the primary tumour (lower third oesophageal/OG versus distal gastric), site of metastases (peritoneal versus other) and exposure to prior chemotherapy (after implementation of amendment).

study treatment

ECX was administered to both treatment groups using the same dose and schedule described previously [11]. Patients randomly assigned to the matuzumab cohort received matuzumab weekly at a dose of 800 mg intravenously over 1 h. A 1-h interval was always observed between completion of the matuzumab infusion and the start of epirubicin administration when both treatments were scheduled on the same day. Treatment cycles were repeated every 3 weeks for a maximum of eight cycles of ECX unless there was evidence of disease progression or unacceptable toxicity, death occurred or consent was withdrawn. Matuzumab was continued as a single agent after the eight cycles of ECX unless there was evidence of disease progression or unacceptable toxicity, death occurred or consent was withdrawn. Patients were followed up until death.

Investigators graded adverse events (AEs) according to National Cancer Institute–Common Toxicity Criteria Version 3.0. AEs and haematological and biochemical values were recorded at each treatment visit. Dose modifications for ECX haematological and non-haematological toxicity have been described previously [7].

Dose modifications for matuzumab were as follows: for grade 1 or 2 hypersensitivity/allergic reaction, the matuzumab infusion rate was reduced to 50% once the reaction had resolved to grade 1 in severity; for grade 3 or 4 reactions, the matuzumab infusion was immediately stopped, the appropriate medical intervention for anaphylaxis was administered and the patient was withdrawn from further matuzumab treatment. For other grade 3 non-haematological and haematological matuzumab-related AEs, the administration of matuzumab was withheld until resolution to grade 1 or less and administration resumed at 100%, 75% and 50% of the original dose on first, second and third occurrence, respectively. In the event of any grade 4 matuzumab-related AE, matuzumab therapy was permanently discontinued. All patients known to have received the study treatment were included in an intention to treat (ITT) analysis for toxic events.

evaluation and outcomes

Pre-screening assessments included complete medical history, physical examination, histopathological confirmation of primary tumour diagnosis and EGFR expression in archived tumour tissue. Evaluation before and during treatment included a complete medical history, physical examination, ECOG performance status, full blood count, serum biochemistry, serum human anti-humanised antibody (for the ECX/ matuzumab group), urinalysis, electrocardiogram, echocardiogram or multiple-gated acquisition scan. A pretreatment chest X-ray and computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen and pelvis were undertaken within 30 days before commencing therapy.
Tumour assessment was undertaken with CT or MRI consistently at 6-week intervals for the first 24 weeks and every 12 weeks thereafter until disease progression. Blinded radiological review was performed by an IRC in addition to local institute assessment. Response was evaluated using the modified World Health Organization (WHO) criteria (Supplementary data, available at Annals of Oncology online). The QOL was assessed with the use of the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire version 3.0 (QLQ.C-30), the EORTC QLQ–OES 18 (the oesophageal module) plus four study-specific questions at the pretreatment, at the fourth chemotherapy visit and at the end-of-treatment visit.

**statistical analysis**

The primary end point was radiologically confirmed tumour response, as assessed by the IRC. On the basis of an objective response rate of 34% for patients receiving ECX, 60 patients were required to show an increase in response rate from 34% to 64% for the matuzumab arm compared with ECX alone arm with 82% power and a one-sided alpha of 0.10. Allowing for a 15% dropout rate led to a planned sample size of 70 patients. The tumour response rates were compared utilising one-sided Fisher’s exact test on the ITT population (patients who have received at least one cycle of matuzumab or any component of ECX). All radiological responses were confirmed by repeat imaging within 4 weeks.

Secondary end points included tumour response as assessed by the investigator, OS, PFS and QOL.

OS was defined as the time from randomisation to death from any cause. PFS was defined as the time from randomisation to the first documented disease progression or death from any cause. Event-related time parameters were estimated using the Kaplan–Meier method and the hazard ratios (HRs) and associated two-sided \( P \)-values were computed using the Cox proportional hazards model. Summary statistics were used for the safety parameters. Changes in global QOL from baseline to best on treatment within each treatment group were evaluated. An interim analysis after \( \sim 60 \% \) of the patients accrued in the study evaluating safety data and investigator observed response rates was conducted using descriptive statistics. This trial is registered with the Clinical Trial Registry, number NCT0021564436.

**role of the funding source**

The funding source Merck KGaA was involved in design, data collection and data analysis of the study but not in interpretation of the findings. SR and DC had full access to all data and DC had the final responsibility to submit for publication.

**results**

From August 2005 to November 2006, a total of 72 patients were entered in a randomised trial: 36 were assigned to ECX/matuzumab and 36 to ECX at 22 centres in the UK and Europe. One patient was withdrawn from the study directly after randomisation due to a poor GFR < 60 ml/min. Thus, the ITT and safety population comprised 71 patients in total: 35 patients received ECX/matuzumab and 36 patients received ECX.

Both study groups were well balanced in terms of baseline characteristics as shown in Table 1. All patients had stage IV metastatic adenocarcinoma. The median number of cycles administered for both study groups was six. The median duration of treatment with ECX was similar for both groups: 127 days versus 134 days for the matuzumab and non-matuzumab groups, respectively. The relative dose intensities for epirubicin and cisplatin were not markedly different between both cohorts (cisplatin \( \geq 80\% \): 83% and 81% for the matuzumab and non-matuzumab groups, respectively; epirubicin \( \geq 80\% \): 77% versus 61% for the matuzumab and non-matuzumab groups, respectively). The most common reason for study treatment discontinuation was disease progression in both groups although this was more frequent with ECX/matuzumab than ECX (80% versus 28%), followed by AEs (6% versus 25%), death (3% versus 6%), withdrawal of consent (3% versus 0%) and others (9% versus 42%).

The primary end point of response, as assessed by the IRC in the ITT population, is shown in Table 2. Objective response rate was lower in the matuzumab group 31%
(95% CI 17–49)—compared with the non-matuzumab group 58% (95% CI 41–74). This difference was not statistically significant in the one-sided Fisher’s exact test $P = 0.994$. Disease control was achieved 60% (95% CI 42–76) in the matuzumab group compared with 75% (95% CI 58–88) in the non-matuzumab group.

Median time to follow-up for survival was 28.5 and 23.0 months for ECX/matuzumab and ECX groups, respectively. At the time of analysis, 22 of 35 (63%) patients had died or progressed and 13 (37%) were censored in the matuzumab group while 25 of 36 (69%) patients had died or progressed and 11 (31%) patients were censored in the non-matuzumab group. There was no relevant difference in the median PFS on the basis of the IRC assessment of the ITT population (Figure 1): 4.8 months (95% CI 2.9–8.1) for the matuzumab group compared with 7.1 months (95% CI 4.4–8.5) for the non-matuzumab group, HR of 1.13 (95% CI 0.63–2.01), $P = 0.678$. Furthermore, no notable difference in the median OS for the ITT population was observed (Figure 2): 9.4 months (95% CI 7.5–16.2) for the matuzumab group compared with 12.2 months (95% CI 9.8–13.8) in the non-matuzumab group, HR of 1.02 (95% CI 0.61–1.70), $P = 0.945$.

The 71 patients in the ITT population formed the safety population for this study. The incidence of the relevant treatment-related AEs in the safety population is shown in Table 3 and the addition of matuzumab to ECX was generally well tolerated. The incidence of neutropenia and febrile neutropenia was similar in both groups. Matuzumab was associated with higher rates of hypokalaemia, nausea, dehydration, pulmonary embolism and skin toxicity. Of the five patients in total in both groups who died within 30 days after the last study drug administration, two patients developed progressive disease while three died due to AEs (cardiac arrest, paralytic ileus and pulmonary embolism) not deemed to be related to the study drug by the investigator.

QLQs were completed by 84%, 60% and 60% of patients at baseline, cycle 4 and end of treatment, respectively. Mean scores on the EORTC QLQ-C30 global health status subscale at baseline, cycle 4 and end of treatment demonstrated a higher baseline score for the non-matuzumab group but no relevant difference between the two groups overall (Table 4).

Fifteen patients (43%) previously enrolled in the ECX group and 15 patients previously (42%) assigned to the matuzumab group received salvage chemotherapy after completion of treatment in this study. Second-line chemotherapy included docetaxel, paclitaxel, irinotecan, FOLFIRI, epirubicin and capecitabine. Three patients in total (one previously enrolled in the non-matuzumab group and two previously assigned to the matuzumab group) received salvage radiotherapy to the site of the primary tumour.

discussion

This randomised phase II study has demonstrated that the combination of matuzumab 800 mg weekly with ECX chemotherapy does not add any significant activity to this regimen with respect to response, PFS and OS. The median PFS and objective response rate of ECX were consistent with those reported in a previous phase III study [11] while the median OS was >11 months, possibly reflecting the use of salvage chemotherapy in >40% of patients.

EGFR overexpression and the associated correlation with poorer prognosis provided a strong rationale for the use of anti-EGFR therapy combined with chemotherapy in advanced...
OG cancer [18–21]. Our previous phase I study demonstrated that the MTD of 800 mg matuzumab weekly combined with standard ECX was associated with acceptable toxicity, encouraging antitumour activity and inhibition of EGFR downstream signalling, which led to this study design [22]. One possible explanation for the negative findings in this study was that the optimum biological dose of matuzumab may not have been reached. The MTD for single agent matuzumab is 1600 mg weekly [23] and the established MTD for matuzumab combined with ECX was 800 mg weekly, with dose-limiting toxicity (DLT) of grade 3 lethargy at higher dose levels [22]. Pharmacodynamic data from our phase I study of ECX plus matuzumab demonstrated EGFR abrogation in skin biopsies at all dose levels of matuzumab evaluated with no dose–response relationship [22]. Thus, it is possible that the optimal biological dose of matuzumab when combined with ECX is >800 mg weekly but this is not feasible to safely administer due to DLT.

This is an important consideration when designing end points for future early-phase trials incorporating biologically targeted cytostatic agents where the maximum biologic effect may occur outside the range of the MTD, unlike cytotoxic drugs [24]. Furthermore, skin biopsies may not be an appropriate surrogate for tumour tissue when evaluating pharmacodynamic data and this needs to be examined further in early development studies of biological agents. The alternative explanation for our findings is that disease progression in these tumours was driven by EGFR-independent mechanisms.

There were no significant differences in dose intensity between the two ECX regimens. There was no significant difference in QOL between the two groups. The incidence and pattern of toxicity for ECX alone were similar to that

Table 3. Most common grade 3/4 treatment-related adverse events in ITT population

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>ECX/matuzumab, N = 35</th>
<th>ECX, N = 36</th>
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<tbody>
<tr>
<td>Neutropenia 13 (37) 12 (33)</td>
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<tr>
<td>Anaemia 2 (6) 2 (6)</td>
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<tr>
<td>Thrombocytopenia 0 1 (3)</td>
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<tr>
<td>Febrile neutropenia 1 (3) 2 (6)</td>
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<tr>
<td>Fatigue/lethargy 7 (20) 5 (14)</td>
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<tr>
<td>Nausea 4 (11) 1 (3)</td>
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<tr>
<td>Vomiting 1 (3) 1 (3)</td>
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<td></td>
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<tr>
<td>Diarrhoea 2 (6) 2 (6)</td>
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<tr>
<td>Dehydration 3 (9) 1 (3)</td>
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<tr>
<td>Palmar plantar 2 (6) 3 (8)</td>
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<tr>
<td>erythrodyssaesetha</td>
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<tr>
<td>Pulmonary embolism 3 (9) 1 (3)</td>
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<tr>
<td>Infection 1 (3) 2 (6)</td>
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<tr>
<td>Hypokalaemia 2 (6) 1 (3)</td>
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<tr>
<td>Hyperkalaemia 1 (3) 1 (3)</td>
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<tr>
<td>Myocardial infarction 1 (3) 2 (6)</td>
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<tr>
<td>Dypnoea 1 (3) 1 (3)</td>
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<tr>
<td>Headache 1 (3) 1 (3)</td>
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<td>Peripheral sensory neuropathy 0 2 (6)</td>
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<tr>
<td>Syncope 2 (6) 0</td>
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<tr>
<td>Skin disordersa 23b (66) 11 (31)</td>
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<tr>
<td>Death within 30 daysb 2 (6) 3 (8)</td>
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aAny grade.
bOnly one grade 3 skin toxicity related to matuzumab.
cDeath within 30 days after the last study drug administration.

ECX, epirubicin, cisplatin and capecitabine.

Figure 2. Kaplan–Meier plot for overall survival. Group A: epirubicin, cisplatin and capecitabine. Group B: epirubicin, cisplatin and capecitabine/ matuzumab.
Table 4. EORTC QLQ-C30 global health status scale, baseline score and best overall change

| Global health status score | ECX/matuzumab | ECX  
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<tbody>
<tr>
<td></td>
<td>Baseline, N = 30</td>
<td>Best overall change, N = 21</td>
</tr>
<tr>
<td>Mean (standard deviation)</td>
<td>53.3 (27.3)</td>
<td>0.0 (28.1)</td>
</tr>
<tr>
<td>Minimum; maximum</td>
<td>0; 100</td>
<td>−33; 75</td>
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EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, quality of life questionnaire version 3.0; ECX, epirubicin, cisplatin and capecitabine.

reported previously [7, 11]. The addition of matuzumab to ECX resulted in a modest increase in the incidence of skin disorders, nausea, hypokalaemia and lethargy. Rash and other skin disorders are well recognised sequelae with the use of anti-EGFR monoclonal antibodies [25, 26] and their incidence in this trial was comparable to previous study reports investigating combination chemotherapy regimens plus matuzumab [27, 28]. Hypokalaemia and hypomagnesaemia have been previously reported following the administration of cetuximab and panitumumab and a magnesium-wasting syndrome is postulated to be associated with lethargy [29–31].

Several single-arm phase II studies investigating combination chemotherapy with cetuximab in this setting have reported objective response rates ranging from 40% to 55% [32–34]. A median time to progression of 5.5 months and median OS of 9.9 months was reported for the combination of cetuximab with FOLFOX-6 in advanced gastric cancer [33]. A study of FOLFIRI plus cetuximab achieved an overall response of 44% and median time to progression of 8 months [35]. However, these findings appear comparable to those reported for ECX chemotherapy (overall response rate 46%, median PFS 6.7 months and median OS 9.9 months) and EOX chemotherapy (overall response rate 48%, median PFS 7.0 months and median OS 11.2 months) in the phase III REAL-2 study [11] and TCF chemotherapy (median time to progression 5.6 months, median OS 9.2 months) in the phase III V325 study [12]. A phase II study of erlotinib in advanced OG cancer demonstrated activity in OGJ tumours but no objective responses in gastric tumours [36]. Recently, the addition of trastuzumab to cisplatin/SFU in human epidermal growth factor receptor 2-positive gastric cancer demonstrated a significant survival benefit in a randomised phase III trial [37].

Despite recent advances, the median OS for advanced OG cancer with combination chemotherapy still only approaches 11 months. Thus, there is a need for novel treatment strategies and the clinical benefit of anti-EGFR therapies needs to be established in randomised phase II/III studies utilising optimal chemotherapy regimens as the reference comparator. However, on the basis of the results of this study, matuzumab does not warrant further evaluation in phase III studies in advanced OG cancer.

acknowledgements

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disclosure

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references


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