Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial

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Summary

Background Docetaxel-based chemotherapy is effective in metastatic gastric and gastro-oesophageal junction adenocarcinoma, but has not yet been evaluated in the context of resectable patients. Here we report findings from the phase 2 part of the phase 2/3 FLOT4 trial, which compared histopathological regression in patients treated with a docetaxel-based triplet chemotherapy versus an anthracycline-based triplet chemotherapy before surgical resection.

Methods In this randomised, open-label, phase 2/3 study, eligible participants were recruited from 28 German oncology centres. Patients with resectable gastric or gastro-oesophageal junction cancer who had clinical stage cT2 or higher, nodal positive (cN+) disease, or both were randomly assigned (1:1) to either three preoperative and three postoperative 3-week cycles of intravenous epirubicin 50 mg/m² on day 1, intravenous cisplatin 60 mg/m² on day 1, and either fluorouracil 200 mg/m² as continuous intravenous infusion or capecitabine 1250 mg/m² orally (two doses of 625 mg/m² per day) on days 1 to 21 (ECF/ECX group) or four preoperative and four postoperative 2-week cycles of docetaxel 50 mg/m², intravenous oxaliplatin 85 mg/m², intravenous leucovorin 200 mg/m², and fluorouracil 2600 mg/m² as a 24 h infusion, all on day 1 (FLOT group). Randomisation was done centrally with an interactive web-response system based on a sequence generated with blocks (block size 2) stratified by Eastern Cooperative Oncology Group performance status, location of primary tumour, age, and nodal status. No masking was done. Central assessment of pathological regression was done according to the Becker criteria. The primary endpoint was pathological complete regression (tumour regression grade TRG1a) and was analysed in the modified intention-to-treat population, defined as all patients who were randomly assigned to treatment excluding patients who had surgery but did not provide resection specimens for central evaluation. The study (including the phase 3 part) has completed enrolment, but follow-up is ongoing and this is an interim analysis. The trial is registered with ClinicalTrials.gov, number NCT01216644.

Findings Between Aug 18, 2010, and Aug 10, 2012, 300 patients (152 patients in the ECF/ECX group; 148 patients in the FLOT group) were enrolled into the phase 2 part of the study, 265 of whom (137 in the ECF/ECX group; 128 in the FLOT group) were assessable on a modified intention-to-treat basis. 119 (93%) of 128 patients in the FLOT group and 126 (92%) of 137 patients in the ECF/ECX group were given all planned preoperative cycles of treatment. FLOT was associated with significantly higher proportions of patients achieving pathological complete regression than was ECF/ECX (20 [16%; 95% CI 10–23] of 128 patients *vs* eight [6%; 3–11] of 137 patients; p=0·02). 44 (40%) of 111 patients in the ECF/ECX group and 30 (25%) of 119 patients in the FLOT group had at least one serious adverse event involving a perioperative medical or surgical complication. The most common non-surgical grade 3–4 adverse events were neutropenia (52 [38%] of 137 patients in the ECF/ECX group *vs* 67 [52%] of 128 patients in the FLOT group), leucopenia (28 [20%] *vs* 36 [28%]), nausea (23 [17%] *vs* 12 [9%]), infection (16 [12%] *vs* 15 [12%]), fatigue (19 [14%] *vs* 11 [9%]), and vomiting (13 [10%] *vs* four [3%]).

Interpretation Perioperative FLOT was active and feasible to administer, and might represent an option for patients with locally advanced, resectable gastric or gastro-eosophageal junction adenocarcinoma.

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Research in context

Evidence before this study

We searched PubMed and the abstracts of major oncology congresses (American Society of Clinical Oncology [ASCO] and ASCO Gastrointestinal Symposium, and European Society for Medical Oncology) from Feb 1, 2016, to July, 25, 2016, with the search terms "gastric", "oesophageal", or "gastro-oesophageal junction cancer" in conjunction with "neoadjuvant" or "perioperative treatment" as well as "pathological regression" or "remission". There were no language or date restrictions. We limited our discussion to trials and reports that we found relevant to the setting of our trial and our population and results.

The prognosis of gastric cancer patients is poor for those with more advanced tumours. Perioperative chemotherapy for gastric cancer and adenocarcinoma of the gastro-oesophageal junction has been established and shown to improve survival in two landmark clinical trials: the MAGIC trial using three 3-week cycles of epirubicin, cisplatin, and fluorouracil (ECF) followed by surgery and three additional ECF cycles and the French FNCLCC/FFCD 9703 study, in which patients received two to three cycles of cisplatin and fluorouracil before and after surgery or surgery alone. However, despite these advances, the outcome of patients with advanced gastric or gastro-oesophageal junction cancer remains unsatisfactory. Docetaxel has proved efficacious in metastatic gastric cancer. Our group has shown the activity and safety of the docetaxel-based triple combination of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), given every 2 weeks in the treatment of patients with metastatic gastric cancer. FLOT treatment resulted in comparatively high proportions of patients achieving pathological complete regression, up to 17% in phase 2 and retrospective studies.

Added value of this study

The study constitutes, to our knowledge, the largest series of prospectively collected data on centrally reviewed pathological complete regression, comparing a perioperative docetaxel-based triplet regimen with an anthracycline-based triplet regimen (standard of care when this study was designed) in resectable gastric and gastro-oesophageal junction cancer. Perioperative FLOT treatment was active and feasible and significantly increased the frequency of complete regression compared with that after ECF/ECX treatment. The favourable activity of FLOT was most pronounced in the intestinal type histology compared with the diffuse type histology and underscores the necessity to consider histology in future trials or when interpreting the results of available data.

Implications of all the available evidence

This study expands the available options for the treatment of resectable, stage II or III gastric and gastro-oesophageal junction adenocarcinoma. Perioperative platinum–fluoropyrimidine doublet regimens such as cisplatin and fluorouracil or triplets such epirubicin, cisplatin, and capecitabine remain appropriate, but FLOT represents an additional option for patients (particularly those with intestinal type tumours), for whom the achievement of pathological regression is considered to be important.

Introduction

The prognosis of gastric cancer patients is poor. Endoscopic or surgical resection is curative in about 90% of early-stage (T1) tumours, but survival drops dramatically for more advanced tumours (T2–4) or those with regional lymph node involvement. In Europe and North America, 5-year overall survival is about 20% for T3/4 tumours.[1] Many investigators around the world have assessed multidisciplinary strategies in an attempt to improve survival. Several therapeutic approaches, including perioperative or neoadjuvant chemotherapy for gastric cancer and adenocarcinoma of the gastro-oesophageal junction, and neoadjuvant chemoradiation therapy for oesophageal or gastro-oesophageal junction cancers, were established.[2–6] The first study to show a survival benefit of perioperative chemotherapy compared with surgery alone was the MAGIC trial.[2] 503 patients with clinical stage II or III adenocarcinoma of the stomach (75%), gastro-oesophageal junction (12%), or lower oesophagus (15%) were treated with either three cycles of epirubicin, cisplatin, and fluorouracil (ECF) before and after surgery or surgery alone. Patients in the chemotherapy group showed a significant improvement in 5-year overall survival compared with surgery only (36% *vs* 23%; p=0·009). In the French FNCLCC/FFCD 9703 phase 3 study,[3] 224 patients with gastro-oesophageal junction (64%), oesophageal (11%), or stomach (24%) adenocarcinoma were enrolled into the study. Patients received two to three cycles of cisplatin and fluorouracil before and after surgery or surgery alone. Patients in the chemotherapy group had significantly improved 5-year overall survival compared with surgery alone (38% *vs* 24%; p=0·02). However, despite these advances, the outcome of patients with advanced gastric or gastro-oesophageal junction cancer remains unsatisfactory. Considerable investigation is still needed to improve perioperative protocols. Furthermore, available studies do not recommend a preferred chemotherapy regimen. Combinations of fluoropyrimidines and platinum with or without an anthracycline have been the most frequently tested regimens. The contribution of adding docetaxel to this combination has not yet been addressed.

Docetaxel has proven efficacy in metastatic gastric cancer, both in first-line and second-line settings. In previous studies,[7,8] our group showed the activity and safety of the docetaxel-based combination consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT), given every 2 weeks in the treatment of patients with

metastatic gastric cancer. We also showed that neoadjuvant FLOT induced high frequencies of pathological complete regression (tumour regression grade TRG1a);[9] 17% after four cycles and 20% after six cycles in patients with resectable disease.[10,11] These proportions were better than those reported for anthracycline-based triplet regimens, which, for example, was 5·6% after four cycles of epirubicin, cisplatin, and capecitabine (ECX) in a phase 2 trial specifically done to explore this endpoint.[12]

These findings provided the rationale for the randomised phase 2/3 FLOT4 trial, which compared ECF or ECX with FLOT as perioperative therapy for patients with potentially resectable adenocarcinoma of the stomach or gastro-oesophageal junction. Here, we present the results of the phase 2 part of the study, which compared histopathological regression in patients treated with either FLOT or ECF/ECX.

Methods

Study design and participants

The FLOT4 study was an investigator-initiated, randomised, open-label, phase 2/3 study done at 28 German oncology centres (appendix p 6).

Patients were eligible if they had histologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction (types I to III) and were regarded as having clinical stage ≥cT2 or nodal positive (cN+) disease as assessed by CT or MRI of the chest, abdomen, and pelvis, and by endoscopic ultrasound. Clinical lymph node positivity was assessed by the treating physicians based on results of the CT, MRI, endoscopic ultrasound, or a combination of modalities. The protocol did not include special criteria for lymph node positivity. Further inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status 0–2, sufficient bone marrow (white blood cell count $>3·0\times10^9$ cells per L and platelet count $>100\times10^9$ cells per L), liver function (total bilirubin ≤1·5×the upper limit of normal [ULN], alanine aminotransferase or aspartate aminotransferase ≤3·5×ULN), cardiac function (ejection fraction of >50% by echocardiography), and kidney function (serum creatinine ≤1·5×ULN, or calculated glomerular filtration rate >50 mL/min), and no concurrent uncontrolled medical illness. Diagnostic laparoscopy was recommended for all patients and mandatory in case of any suspicion of peritoneal involvement (applicable standard of care in Germany). Bone scintigraphy was mandatory in case of suspected bone metastases. Patients were excluded if they had distant metastases, infiltration of adjacent structures or organs, or had previously received tumour resection, chemotherapy, or radiation therapy. There was no age limit and no minimum estimated life expectancy for eligible patients, because the study was done in potentially curable patients. Comorbidities that were not permitted were active coronary heart disease, cardiomyopathy or congestive heart failure of stage 3 or 4 according to New York Heart Association Functional Classification, and inflammatory bowel disease.

Informed consent and all versions of study protocol were approved by the central ethics committee (Landesärztekammer Hessen) and the ethics committees of each participating institution. The study was done according to the Declaration of Helsinki and Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation. Study management and coordination was done by the Institute of Clinical Cancer Research (Frankfurt, Germany), data management was done by Trium Analysis Online (Munich, Germany), and onsite monitoring was done by MCA (Berlin, Germany). All participants gave written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned (1:1) centrally to surgical resection with either perioperative ECF or ECX or perioperative FLOT with an interactive web-response system based on a sequence generated with blocks (size 2) stratified by ECOG performance status (0 or 1 *vs* 2), location of primary tumour (gastro-oesophageal junction type I *vs* gastro-oesophageal junction type II/III *vs* stomach), age (<60 years *vs* 60–69 years *vs* ≥70 years), and suspected lymph node involvement (N+ *vs* N–). Patients were enrolled by authorised individuals who requested randomisation with an interactive web-response system integrated in the electronic case report forms. Assignment to trial groups took place on the server of the independent data management providers (Trium Analysis Online, Munich, Germany) using a validated assignment program, which underlies strict access control. The randomisation system allocated every patient a unique identification number and sent a message including allocation result to the investigator. The study was open-label and no masking was required. Notably, the relatively high number of stratification factor used (four) was selected because of the potential transition to phase 3.

Procedures

Perioperative ECF or ECX was administered for three preoperative cycles followed by three postoperative cycles. Each 3-week cycle consisted of epirubicin 50 mg/m² intravenously on day 1, cisplatin 60 mg/m² intravenously on day 1, and fluorouracil 200 mg/m² as continuous intravenous infusion on days 1 to 21. Fluorouracil could be replaced by capecitabine 1250 mg/m² given orally (two doses of 625 mg/m² per day) on days 1 to 21 upon investigator's choice.[13] Perioperative FLOT was given for four preoperative cycles followed by four postoperative cycles. Each 2-week cycle consisted of docetaxel 50 mg/m² intravenous on day 1, oxaliplatin 85 mg/m² intravenous on day 1, leucovorin 200 mg/m² intravenous on day 1, and fluorouracil 2600 mg/m² as 24 h infusion on day 1. Antiemetic prophylaxis and other supportive therapies could be given according to local protocols. Growth

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See Online for appendix

factors were recommended as secondary prophylaxis for patients who had febrile neutropenia or treatment interruptions because of neutropenia or leucopenia. Dose reductions of docetaxel and oxaliplatin (FLOT group) or cisplatin and epirubicin (ECF/ECX group) to 75% were done in patients who had febrile neutropenia (despite the use of granulocyte-colony stimulating factor [G-CSF]), thrombocytopenia causing bleeding, or any other haematological dose-limiting toxicities, and to 50% if toxicities recurred after the first dose reduction. The dose of all drugs was reduced to 75% for non-haematological toxicities exceeding National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) grade 2, and to 50% if toxicities recurred after the first dose reduction. The dose of oxaliplatin was adjusted for sensory peripheral neuropathy as published previously.[7] Dose adjustments for certain drugs for specific toxicities were permitted at the investigator's discretion. Criteria for stopping treatment were unacceptable toxicity, disease progression or death, patient's request, or investigator's decision that stopping treatment was in the best interest of the patient.

At baseline and before the start of every cycle, patients were assessed according to medical history, physical examination, weight, ECOG performance status, complete blood count, and blood chemical tests and any adverse events were reported. Restaging by means of CT or MRI and endoscopy was done before surgical treatment to exclude disease progression or distant metastases, and then every 3 months until disease progression, relapse, or death. Surgery was scheduled 3 weeks after completion of the last cycle of preoperative chemotherapy. The type of surgical procedure was determined by location and extent of the primary tumour. According to the study protocol, transthoracic oesophagectomy with resection of the proximal stomach and two-field (mediastinal and abdominal) lymphadenectomy was done for type I gastro-oesophageal junction cancers and gastrectomy with transhiatal distal oesophagectomy plus D2 lymphadenectomy was done for type II and III gastro-oesophageal junction cancers. For gastric cancer, total or subtotal distal gastrectomy with D2 lymphadenectomy was done, which is standard of care in Germany. Surgeons had to be specialised abdominal surgeons (thoracoabdominal surgery is usually done by abdominal surgeons in Germany). The principal investigator trained the surgeons in the protocol requirements. Patient's pathology and surgery reports were collected and reviewed centrally. In case of non-compliance with the protocol, corrective measures were initiated (eg, retraining of the surgeon).

The resected specimens were embedded into paraffin after formalin fixation according to standard guidelines. The specimens were sent to central pathology and reviewed by an experienced pathologist (AT) who was masked to treatment group and clinical stage. Histopathological tumour regression in the primary tumour and, separately, in resected lymph nodes was assessed. Examination of resection specimens included measurement of the macroscopically identifiable residual tumour or scarring indicating the site of the previous tumour bed. Specimens were stained with haematoxylin and eosin, Elastica van Gieson, and periodic acid-Schiff to detect tumour desmoplasia, scarring, and signet-ring cells. If necessary, supplementary immunohistochemical investigations were used to identify tumour cells. In case of an absence of tumour cells in the resection sample, a complete histopathological work-up of the suspected original tumour bed was done.

Tumour regression grade was quantified using the Becker regression criteria,[9] which are based on the estimation of the percentage of vital tumour cells in relation to the macroscopically identifiable tumour bed and include the following categories: TRG1a (equivalent to pathological complete regression; no residual tumour cells); TRG1b (subtotal regression; <10% residual tumour cells); TRG2 (partial regression; 10–50% residual tumour cells); and TRG3 (minor or no regression; >50% residual tumour cells).[9,14] The tumour bed was identified by signs of tumour regression, such as marked fibrosis, necrosis, flattening of the mucosa, or the presence of macrophages. The expanse of vital tumour cells was established and semi-quantitatively related to the tumour bed as a percentage value. Lymph nodes without any signs of metastatic involvement were regarded to be tumour free. In case of fibroses or acellular mucin lakes, the lymph nodes were diagnosed as tumour free and regression changes were recorded separately.

Pathological staging, including depth of tumour invasion (T), lymph node involvement (N), and resection status (RX, R0, or R1), was done by the local pathologist according to the 7th edition of the TNM International Union Against Cancer (UICC) classification. The histological type according to Lauren[15] was assessed by the local pathologist in the pretherapeutic biopsy.

Serious adverse events and perioperative morbidity and mortality were regularly monitored and reported to the independent data safety monitoring board and the responsible authorities.

Outcomes

The primary endpoint for the phase 2 part of the study was proportion of patients with pathological complete regression in the primary tumour, defined as the proportion of patients with pathological complete regression (TRG1a) over the total number of patients evaluated centrally by the study pathologist. Secondary endpoints of the phase 2 part were proportion of patients with margin-free resection (R0, as assessed by the local pathologist); disease-free survival (time from randomisation to disease progression or death from any cause); overall survival (defined as time from randomisation to death from any cause); correlation of

pathological complete regression with disease-free survival and overall survival; perioperative toxicity, morbidity, and mortality; and non-surgical adverse events according to the CTCAE version 3.0. Since the phase 2 part of the study was planned to potentially transition into phase 3, the phase 2 part was first analysed according to a separate study analysis plan, which included the primary endpoint and selected secondary endpoints (margin-free resection, serious adverse events of perioperative morbidity, and 30-day mortality rate) and other data (chemotherapy administration, types of surgical resection, and post-operative TNM stages). These endpoints and data were selected because they were important for decision making on a potential transition into phase 3 and for the interpretation of the primary endpoint. Other secondary endpoints related to survival such as overall survival or disease-free survival were not to be analysed unless a transition into phase 3 had been excluded to avoid alpha

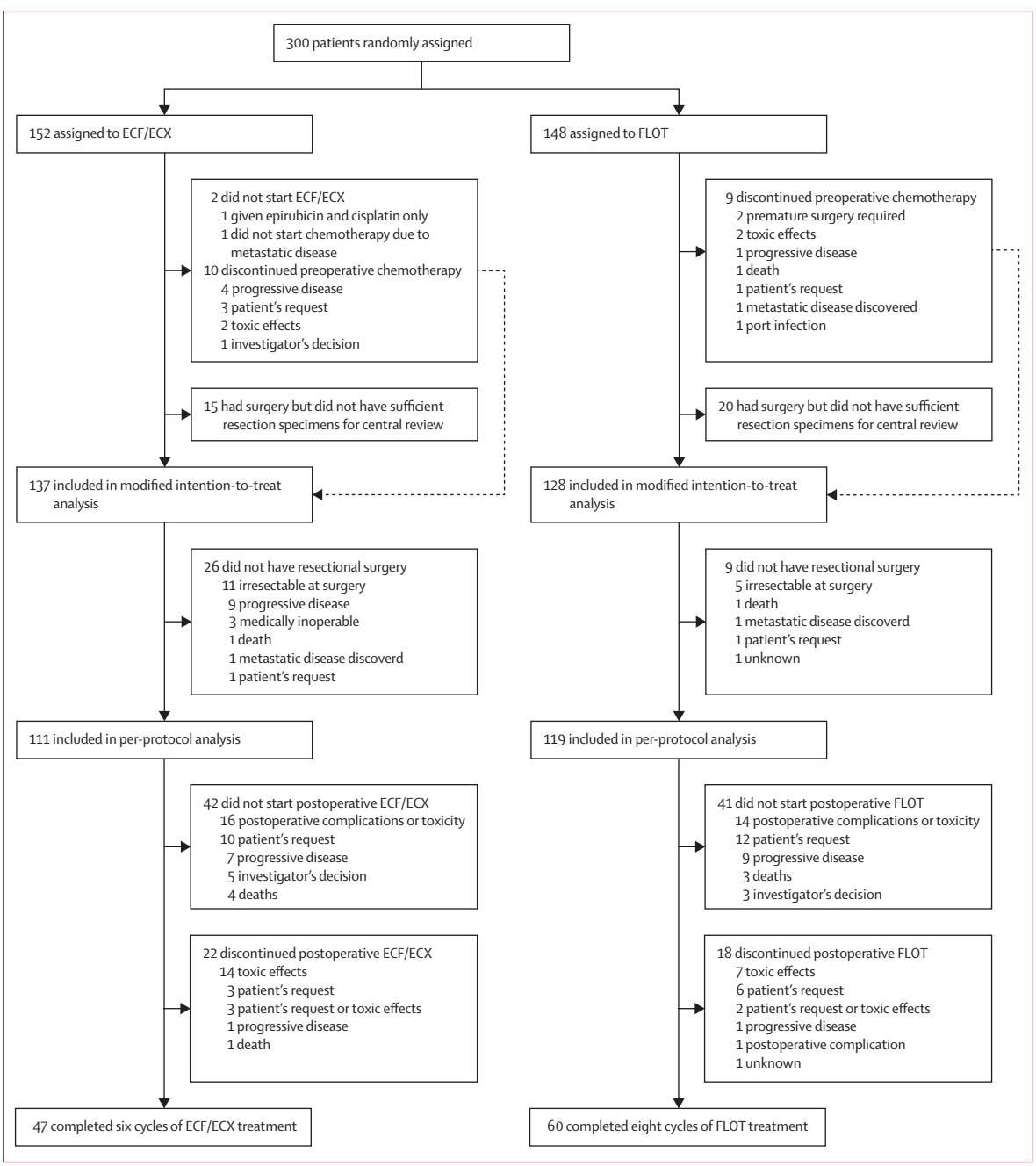

***Figure 1*: Trial profile**
ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel.

spending in phase 3, and because the follow-up time was insufficient to correctly assess these endpoints. The analysis based on the study analysis plan, which is reported in this manuscript, resulted in a transition into phase 3. Results from the phase 3 part will be published elsewhere.

Statistical analysis

The sample size calculation of the phase 2 part of the study was based on the assumption that the proportion of patients achieving a pathological complete regression would be 5% with ECF/ECX and 15% with FLOT.[10,12] 300 patients was calculated to provide 80% power to detect this improvement in pathological complete regression (one-sided significance level of $p<0·05$; Fisher's exact test), including a 15% dropout. A transition into a phase 3 trial was planned if FLOT proved superior to ECF/ECX in terms of pathological complete regression.

	ECF/ECX (n=137)	FLOT (n=128)
Age (years)	62 (52–69)	62 (54–69)
<60	60 (44%)	54 (42%)
60–69	45 (33%)	43 (34%)
>70	32 (23%)	31 (24%)
Sex		
Male	100 (73%)	102 (80%)
Female	37 (27%)	26 (20%)
ECOG performance status		
0	90 (66%)	80 (63%)
1	46 (34%)	48 (38%)
2	1 (1%)	0
Primary tumour location		
Gastric	59 (43%)	67 (52%)
Gastro-oesophageal junction type I	35 (26%)	33 (26%)
Gastro-oesophageal junction type II	37 (27%)	22 (17%)
Gastro-oesophageal junction type III	6 (4%)	6 (5%)
Clinical tumour stage		
cT3/T4	113 (82%)	104 (81%)
cT1/T2	24 (18%)	23 (18%)
cTx	0	1 (1%)
Clinical node stage		
cN+	110 (80%)	98 (77%)
cN–	27 (20%)	30 (23%)
Lauren's classification		
Intestinal	60 (44%)	52 (41%)
Diffuse	39 (28%)	34 (27%)
Mixed	7 (5%)	11 (9%)
Unknown or unclassifiable	31 (23%)	31 (24%)

Data are n (%) or median (IQR), unless otherwise indicated. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. ECOG=Eastern Cooperative Oncology Group.

***Table 1*: Baseline characteristics of the modified intention-to-treat population**

The primary endpoint was analysed in the modified intention-to-treat (ITT) population, defined as all patients who were randomly assigned to a treatment, regardless of whether they had surgery, excluding patients who were resected but did not provide resection specimens for central evaluation. Because of the exclusion of patients without resection specimens, we refer to this population as the modified ITT population. The primary endpoint was additionally assessed in a prespecified sensitivity analysis in the per-protocol population. This population was defined as all patients who were resected and provided resection specimens for central evaluation (the subgroup of the modified ITT that underwent resection). Regression by preoperative Lauren classification was done in the modified ITT population excluding patients with unknown or unclassifiable tumours with the modified Wald method.

Non-surgical adverse events and serious adverse events were analysed in the modified ITT population. Post-operative TNM stages, serious adverse events of peri-operative morbidity, and 30-day mortality rate were analysed in the per-protocol population (resected patients). Comparisons of surgery type, resection type, and TNM stage were post-hoc analyses. Data were analysed with SAS (version 9.3). p values were calculated using Fisher's exact test, unless otherwise indicated and all p values presented are two-sided, unless otherwise indicated.

This study is registered with ClinicalTrials.gov, number NCT01216644.

Role of the funding source

The funders had no role in study design (phase 2 part), data collection, data analysis, data interpretation, or writing of the report and had no access to the raw data. S-EA-B, CP, and TG had access to the raw data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 18, 2010, and Aug 10, 2012, 300 patients (152 patients in the ECF/ECX group; 148 patients in the FLOT group) were enrolled into the phase 2 part of the FLOT4 trial. We were unable to collect the resection specimens for central pathology review in 35 patients (12% of all randomised patients) who were resected (figure 1). The most frequent reason that specimens were not available for central evaluation was refusal of the local pathologist to send all resection specimens (nine of 15 patients in the ECF/ECX group; 13 of 20 patients in the FLOT group). These patients were excluded from the analyses. Therefore, the modified ITT population consisted of 265 patients (137 patients in the ECF/ECX group; 128 patients in the FLOT group). 35 of 265 patients did not undergo surgical resection (26 in the ECF/ECX group; nine in the FLOT group); thus, 230 patients were assessed on a per-protocol basis (figure 1).

The baseline characteristics of the modified ITT population are shown in table 1. 126 (48%) of 265 patients had stomach tumours and 139 (52%) had gastro-oesophageal junction cancers. Treatment groups were well balanced for histological types by Lauren's classification. Baseline characteristics of all 300 patients randomly assigned to a treatment are shown in the appendix (p 1).

Preoperative chemotherapy data were available for all 265 patients in the modified ITT population. In the ECF/ECX group, 85 (62%) of 137 patients received capecitabine (ECX) and 50 (37%) of 137 patients received fluorouracil (ECF). The median number of preoperative cycles was three (range 0–3) in the ECF/ECX group and four (range 1–4) in the FLOT group. 126 (92%) of 137 patients in the ECF/ECX group and 119 (93%) of 128 patients in the FLOT group completed all recommended cycles of preoperative chemotherapy (figure 1).

69 (50%) of 137 patients in the ECF/ECX group and 78 (61%) of 128 patients in the FLOT group started postoperative chemotherapy. 47 (34%) of 137 patients in the ECF/ECX group finished the study according to protocol (six cycles) compared with 60 (47%) of 128 patients in the FLOT group (eight cycles). Reasons for not starting or discontinuing postoperative chemotherapy are shown in figure 1. More patients had surgical resection in the FLOT group (119 [93%] of 128 patients) than in the ECF/ECX group (111 [81%] of 137 patients; table 2). Reasons for not proceeding to surgery were progression of disease or death in 11 patients, metastatic disease detected after randomisation in two patients, irresectability detected during surgery in 16 patients, patient request in two cases, medical inoperability in three patients, and an unknown reason in one patient (figure 1). The type of surgical procedures and lymph node dissections done in the study, and the resulting pathological tumour stage and nodal status are shown in table 2. D1 lymph node dissection was done in ten patients, mostly because of incurability findings during surgery, such as peritoneal carcinomatosis (six of ten patients). 16 D3 lymph node dissections were done based on the surgeon's decision. In the postoperative staging, a greater proportion of patients had low pathological tumour stage (<ypT3) and low pathological nodal stage (<ypN2) in the FLOT group than in the ECF/ECX group (table 2).

The results for pathological regression are shown in table 3 and the appendix (p 2). In the modified ITT population, a significantly higher proportion of patients achieved a pathological complete regression (TRG1a) in the FLOT group than in the ECF/ECX group (20 [16%; 95% CI 10·3–23·0] of 128 patients in the FLOT group *vs* eight [6%; 2·8–11·3] of 137 patients in the ECF/ECX group; p=0·02). The proportion of patients who achieved complete and subtotal regression (TRG1a/b) was also higher with FLOT (47 [37%] of 128 patients, 95% CI 28·9–45·4%) than with ECF/ECX (31 [23%] of 137 patients, 16·4–30·4%; p=0·02). In the per-protocol population, comprising only resected patients with resection specimens available, 20 (17%; 95% CI 11·1–24·6%) of 119 patients in the FLOT group achieved a TRG1a compared with eight (7%; 3·5–13·8%) of 111 patients in the ECF/ECX group (p=0·03). All eight patients with TRG1a in the ECF/ECX group had tumour-free lymph nodes (ypN0). Two of 20 patients with TRG1a in the FLOT group had histopathological signs of lymph node involvement (ypN1), one of which was classified as nodal pathological complete regression (nodal TRG1a) and one as modal partial regression (nodal TRG 2).

	ECF/ECX n/N*	FLOT n/N*	p value†
Type of surgery			
Gastrectomy (total or subtotal)	48/137 (35%)	61/128 (48%)	0·046
Gastrectomy and transhiatal oesophagectomy	31/137 (23%)	25/128 (20%)	0·55
Transthoracic oesophagectomy	32/137 (23%)	33/128 (26%)	0·67
No surgery‡	26/137 (19%)	9/128 (7%)	0·01
Lymphadenectomy			
D1	5/111 (5%)	5/119 (4%)	1·00
D2	58/111 (52%)	70/119 (59%)	0·35
D3	9/111 (8%)	7/119 (6%)	0·61
1-field	1/111 (1%)	2/119 (2%)	1·00
2-field	31/111 (28%)	29/119 (24%)	0·55
3-field	5/111 (5%)	6/119 (5%)	1·00
Missing data	2/111 (2%)	0	0·23
Resection grade			
R0 resection (ITT)	101/137 (74%)	109/128 (85%)	0·02
R1/Rx resection	10/137 (7%)	10/128 (8%)	1·00
No surgery‡	26/137 (19%)	9/128 (7%)	0·01
Pathological tumour stage (ypT)			
ypT0	7/111 (6%)	19/119 (16%)	0·02
ypT1	7/111 (6%)	20/119 (17%)	0·01
ypT2	16/111 (14%)	13/119 (11%)	0·44
ypT3	62/111 (56%)	56/119 (47%)	0·19
ypT4	19/111 (17%)	11/119 (9%)	0·08
Combined ypT0/ypT1/ypT2	30/111 (27%)	52/119 (44%)	0·01
Combined ypT3/ypT4	81/111 (73%)	67/119 (56%)	0·01
Pathological nodal stage (ypN)			
ypN0 (no regional lymph nodes)	59/111 (53%)	70/119 (59%)	0·43
ypN1 (1–2 positive lymph nodes)	14/111 (13%)	20/119 (17%)	0·46
ypN2 (3–6 positive lymph nodes)	21/111 (19%)	12/119 (10%)	0·06
ypN3 (>6 positive lymph nodes)	17/111 (15%)	17/119 (14%)	0·85
ypN0/N1	73/111 (66%)	90/119 (76%)	0·11
ypN2/N3	38/111 (34%)	29/119 (24%)	0·11

Data are n/N (%). ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. 1-field=mediastinal lymphadenectomy. 2-field=mediastinal and abdominal lymphadenectomy. 3-field=mediastinal, abdominal, and cervical lymphadenectomy. R0=margin-free resection. ITT=intention to treat. R1=microscopic margins are positive. Rx=resectional status was not evaluable. *Populations analysed in the table are: ITT (n=137 for ECF/ECX, n=128 for FLOT); per-protocol or resected patients (n=111 for ECF/ECX, n=119 for FLOT). †p values compare percentages for ECF/ECX with those for FLOT in the corresponding table row. ‡Five patients in the ECF/ECX group and two patients in the FLOT group who had non-resectional surgery, and 21 patients in the ECF/ECX group and seven patients in the FLOT group who did not proceed to surgery at all.

***Table 2*: Surgical and pathology results**

	ECF/ECX (n=137)	95% CI	FLOT (n=128)	95% CI	p value*
Complete (TRG 1a)†	8 (6%)	2·8–11·3%	20 (16%)	10·3–23·0%	0·02
Subtotal (TRG 1b)	23 (17%)	11·4–24·0%	27 (21%)	14·9–29·0%	..
Complete or subtotal (TRG 1a/b)	31 (23%)	16·4–30·4%	47 (37%)	28·9–45·4%	0·02
Partial (TRG 2)	28 (20%)	14·5–28·0%	23 (18%)	12·2–25·6%	..
Minimal or none (TRG 3)	52 (38%)	30·3–46·3%	49 (38%)	30·3–46·9%	..
No surgery	26 (19%)	13·2–26·4%	9 (7%)	3·6–13·0%	..

Data are n (%). ITT=intention-to-treat. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. TRG=tumour regression grade. *ECF/ECX compared with FLOT. †TRG1a was achieved in eight (7%) of 111 patients who had ECF/ECX and 20 (17%) of 119 patients who had FLOT (p=0·03) in the per-protocol population (resected patients).

***Table 3*: Histopathological tumour regression in the modified ITT population according to Becker**

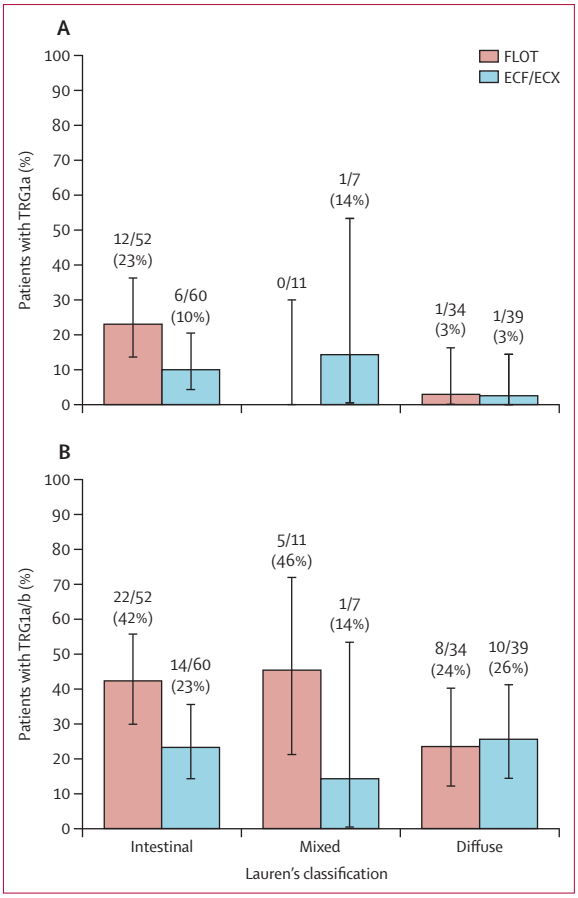

***Figure 2*: Histopathological regression by Lauren's classification**
(A) Complete histopathological regression (TRG1a) and (B) complete and subtotal histopathological regression (TRG1a/b) by treatment group according to Lauren's classification subtype. Bars show 95% CI. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. TRG=tumour regression grade.

In the modified ITT population, margin-free resection (R0) was achieved in 109 (85%) of 128 patients in the FLOT group and 101 (74%) of 137 patients in the ECF/ECX group. In the per-protocol population of only resected patients with resection specimens available, margin-free resection was achieved in similar numbers of patients in both groups: 109 (92%) of 119 in the FLOT group and 101 (91%) of 111 in the ECF/ECX group.

We related tumour regression grade to Lauren's classification. 203 (77%; 97 in the FLOT group, 106 in the ECF group) of the 265 modified ITT patients were classified according to Lauren's classification and were included in this analysis. In the pooled population of both groups, we found that TRG1a status was most frequent in patients with intestinal type tumours (18 [16%] of 112 patients) and least frequent in patients with the diffuse type histology (two [3%] of 73 patients; p=0·004), whereas one (6%) of 18 patients had TRG1a in the mixed type histology (p=0·47). When analysed according to treatment group, 12 (23%) of 52 patients in the FLOT group and six (10%) of 60 patients in the ECF/ECX group had TRG1a in intestinal type tumours (p=0·07; figure 2). In patients with diffuse type histology, one (3%) of 34 patients in the FLOT group and one (3%) of 39 patients in the ECF/ECX group had TRG1a (p=1). In patients with mixed histology, none of 11 in the FLOT group and one of seven in the ECF/ECX group achieved TRG1a (p=0·4). The proportion of patients who achieved TRG1a/b was greater in the FLOT group than in the ECF/ECX group for those with intestinal type histology (p=0·04). The proportion of patients with mixed histology and diffuse type histology who achieved a TRG1a/b was similar between groups (mixed: p=0·4, diffuse type: p=1).

Pathological complete regression was achieved in ten (15%) of 67 patients with gastric primary tumours and ten (16%) of 61 patients with gastro-oesophageal junction primary tumours in the FLOT group, and in five (9%) of 59 patients with gastric primary tumours and three (4%) of 78 patients with gastro-oesophageal junction primary tumours in the ECF/ECX group. In the pooled population of both groups, frequency of resection, R0 resection, and pathological complete regression were similar between the two primary tumour locations (appendix pp 3–4).

44 (40%) of 111 patients in the ECF/ECX group and 30 (25%) of 119 patients in the FLOT group had at least one serious adverse event that involved a perioperative medical or surgical complication (table 4). The 30-day mortality rate was four (4%) of 111 patients in the ECF/ECX group and two (2%) of 119 patients in the FLOT group. Non-surgical serious adverse events were reported in 65 (47%) of 137 patients in the ECF/ECX group and 53 (41%) of 128 patients in the FLOT group. The most frequent serious adverse events in the FLOT group were neutropenia (seven [6%] of 128 patients) and infection (seven of [6%] of patients). In the ECF/ECX group, the most frequent serious adverse event was infection (11 [8%] of 137 patients). The most common non-surgical grade 3–4 adverse events were neutropenia (52 [38%] of 137 patients in the ECF/ECX group *vs* 67 [52%] of 128 patients in the FLOT group), leucopenia (28 [20%] *vs* 36 [28%]), nausea (23 [17%] *vs* 12 [9%]), infection (16 [12%]

vs 15 [12%]), fatigue (19 [14%] *vs* 11 [9%]), and vomiting (13 [10%] *vs* four [3%]; table 5).

Dose modifications were done in 57 (42%) of 137 patients in the ECF/ECX group and 50 (39%) of 128 patients in the FLOT group. In the ECF/ECX group, 35 (26%) of 137 patients had preoperative modifications and 22 (16%) of 137 patients had postoperative modifications. In the FLOT group, 23 (18%) of 128 patients had preoperative modifications and 27 (21%) of 128 patients had postoperative modifications. Treatment discontinuations at the patient's request because of drug-related toxicity occurred in 19 (14%) of 137 patients in the ECF/ECX group and ten (8%) of 128 patients in the FLOT group. The adverse events and grades that led to treatment discontinuations are shown in the appendix (p 5). One patient in the ECF/ECX group died from a treatment-related adverse event (septic infection). Nine patients died during the study treatment in the ECF/ECX group (septic infection, n=1; disease progression, n=1; surgical mortality, n=7) and four patients died in the FLOT group (disease progression, n=1; surgical mortality, n=2; unknown, n=1).

	ECF/ECX (n=111)	FLOT (n=119)
Patients with at least one serious adverse event involving a perioperative morbidity	44 (40%)	30 (25%)
Type of complication*		
Medical complication	17 (15%)	16 (13%)
Anastomotic leak	12 (11%)	8 (7%)
Wound healing disorder	5 (5%)	3 (3%)
Pneumonia	5 (5%)	3 (3%)
Pleural complication	5 (5%)	3 (3%)
Infection	4 (4%)	4 (3%)
Intestinal occlusion	4 (4%)	0
Sepsis	2 (2%)	1 (1%)
Abscess	2 (2%)	2 (2%)
Bleeding	0	1 (1%)
Surgical complication other†	3 (3%)	1 (1%)

Data are n (%). ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. *The sum is more than 100% because some patients had more than one severe perioperative complication. †One patient (ECF/ECX) had colon reposition and segment resection; one patient (ECF/ECX) had organ perforation; one patient (ECF/ECX) had retention in the upper abdomen; and one patient (FLOT) had relaparatomy, necrosectomy, and pancreatitis.

***Table 4*: Serious adverse events with perioperative morbidity**

Discussion

The phase 2 part of the FLOT4 trial constitutes, to our knowledge, the largest series of prospectively collected data on centrally reviewed pathological complete regression, comparing a docetaxel-based triplet with an anthracycline-based triplet in the perioperative therapy of gastric and gastro-oesophageal junction cancer. The observed proportion of patients who achieved TRG1a with FLOT treatment versus ECF/ECX confirmed our hypothesis that FLOT treatment would result in an increased chance of pathological complete regression by approximately 10%.

The proportion of patients achieving pathological complete regression with ECF/ECX in this study (6%) is in line with results from a phase 2 trial[12] in localised gastro-oesophageal junction cancer, which showed that 6% of 34 patients had pathological complete regression after four cycles of preoperative ECX. Although small, this study is of interest because pathological complete regression was the primary endpoint and was evaluated centrally. The proportion of patients is also consistent with results from large randomised trials investigating the ECX regimen. The OEO5[16] and ST03 trials[17] showed a Mandard TRG1 rate (corresponds to TRG1a according to Becker) of 7% and 8% for ECX, respectively, when analysed in the intention-to-treat population. The proportion of patients who achieved a TRG1a or TRG1b with ECF/ECX, which was 23% in our study, is also in line with previous reports.[17] Thus, our study does not under-report tumour regression proportions for ECF/ECX. Notably, limitations exist in the cross-trial comparisons. The tumour regression data from the OEO5 and the ST03 trials were based on local pathology and different TRG systems were used (Becker *vs* Mandard).[9,18] Nevertheless, both grading systems are accepted classifications and distinguish between responders with complete and subtotal regression (Becker 1a or 1b; Mandard 1 or 2) and non-responders with partial or no regression (Becker 2 or 3; Mandard 3–5).[14,19] Likewise, the proportion of patients achieving a pathological complete regression with FLOT (16%) is in line with results reported with docetaxel-based triplet regimens in small, non-randomised studies,[11,20,21] and pooled[22] and retrospective[10] analyses. The proportion of patients who achieved pathological complete regression in these studies ranged between 14%[10] and 20%.[11] Notably, the number of patients who achieved pathological complete regression with FLOT falls in the range of response seen with chemoradiation for gastro-oesophageal junction tumours. For instance, a German phase 3 trial[23] showed that 16% of patients with adenocarcinoma of the gastro-oesophageal junction achieved pathological complete regression with induction chemotherapy followed by chemoradiation.

Whether pathological regression is a prognostic marker for survival outcomes in gastric and gastro-oesophageal junction cancer is an important question. There has been a general debate about this, but compelling evidence supports the use of tumour regression as a predictive parameter for survival.[14,16,17,24] For example, the study by Becker and colleagues,[14] comprising 480 patients, showed that tumour regression, defined as complete or subtotal regression (TRG1a or TRG1b), was a prognostic factor and was independent from ypT and ypN stage in patients who had neoadjuvant platinum-based chemotherapy. The OEO5[16] and ST03 trials[17] provided strong additional

	ECF/ECX (n=137)			FLOT (n=128)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Gastrointestinal disorders						
Nausea	81 (59%)	23 (17%)	0	78 (61%)	12 (9%)	0
Vomiting	40 (29%)	12 (9%)	1 (1%)	38 (30%)	4 (3%)	0
Stomatitis	46 (34%)	6 (4%)	0	39 (30%)	2 (2%)	0
Diarrhoea	38 (28%)	7 (5%)	2 (1%)	68 (53%)	9 (7%)	0
Constipation	33 (24%)	0	0	26 (20%)	1 (1%)	0
Decreased appetite	11 (8%)	2 (1%)	0	9 (7%)	0	0
Dysphagia	6 (4%)	1 (1%)	0	9 (7%)	2 (2%)	0
Blood and lymphatic system disorders						
Anaemia	112 (82%)	8 (6%)	0	109 (85%)	1 (1%)	0
Leucopenia	73 (53%)	20 (15%)	8 (6%)	65 (51%)	26 (20%)	10 (8%)
Neutropenia	39 (28%)	34 (25%)	18 (13%)	28 (22%)	32 (25%)	35 (27%)
Thrombocytopenia	49 (36%)	5 (4%)	1 (1%)	50 (39%)	1 (1%)	0
Febrile neutropenia	NA	1 (1%)	0	NA	6 (5%)	0
Cardiac, pulmonary, and thrombotic events						
Thromboembolic* events	9 (7%)	8 (6%)	0	5 (4%)	4 (3%)	0
Cardiac complications†	6 (4%)	2 (1%)	1 (1%)	2 (2%)	0	1 (1%)
Dyspnoea	4 (3%)	3 (2%)	0	6 (5%)	2 (2%)	0
General and other disorders						
Neurotoxic effects	38 (28%)	3 (2%)	1 (1%)	83 (65%)	10 (8%)	0
Fatigue	71 (52%)	18 (13%)	1 (1%)	80 (63%)	11 (9%)	0
Alopecia‡	86 (63%)	NA	NA	86 (67%)	NA	NA
Pain	68 (50%)	5 (4%)	0	64 (50%)	5 (4%)	1 (1%)
Renal impairment§	47 (34%)	1 (1%)	1 (1%)	16 (13%)	0	0
Hand-foot syndrome	21 (15%)	7 (5%)	0	17 (13%)	0	0
Weight decreased	19 (14%)	4 (3%)	0	18 (14%)	0	1 (1%)
Fever	17 (12%)	1 (1%)	0	30 (23%)	2 (2%)	0
Infection	13 (9%)	15 (11%)	1 (1%)	14 (11%)	15 (12%)	0
Skin effects¶	15 (11%)	0	0	9 (7%)	0	0
Worsening of general condition	6 (4%)	3 (2%)	0	4 (3%)	2 (2%)	1 (1%)
Auditory impairment	2 (1%)	1 (1%)	0	2 (2%)	0	0
Laboratory						
GPT elevation	20 (15%)	0	0	56 (44%)	2 (2%)	1 (1%)
GOT elevation	18 (13%)	0	0	56 (44%)	1 (1%)	0
ALP elevation	17 (12%)	0	0	28 (22%)	0	0

Data are n (%), unless otherwise indicated. Data show adverse events of grade 1–2 occurring in more than 10% of patients and all grade 3 or 4 adverse events. One treatment-related death due to sepsis was noted in the ECF/ECX group. Some grades are not applicable for febrile neutropenia and alopecia; febrile neutropenia can only be grade 3 or 4 and alopecia can only be grade 1 or 2. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. NA=not applicable. GPT=glutamic-pyruvic transaminase. GOT=glutamate oxaloacetate transaminase. ALP=alkaline phosphatase. *Includes pulmonary embolism and deep vein thrombosis †Includes cardiac ischaemia, cardiac arrhythmias, other functional cardiac disorders. ‡Includes n=27 (20%) grade 2 alopecia in the ECF group and n=31 (24%) grade 2 alopecia in the FLOT group. §Functional impairment, including creatinine elevation. ¶Includes dry skin and other skin disorders.

Table 5: **Adverse events**

evidence supporting pathological regression as a prognostic factor. Therefore, in our opinion, histopathological regression (complete or complete and subtotal) can be considered as an appropriate endpoint for neoadjuvant phase 2 trials in gastric and gastro-oesophageal junction cancer. Histopathological regression could be less susceptible to selection bias and less dependent on the quality of surgical resection compared with other endpoints, such as microscopically complete resection (R0). Moreover, histopathological regression retains discriminative power even if only patients with easily resectable tumours are recruited into the study. As an early endpoint for predicting efficacy, histopathological regression could help to accelerate the process of testing new therapies. However, further research is still needed to define the role of pathological regression as an endpoint for phase 3 trials more clearly. It remains unclear how much improvement in histopathological regression is needed to achieve substantial increases in survival. In the OE05 trial,[16] a slight (5% in the ITT population) improvement of pathological complete regression with neoadjuvant ECX versus CF for potentially resectable oesophageal and gastro-oesophageal junction adenocarcinoma did not improve survival, although some improvement in progression-free survival was seen.

Favourable pathological regression with FLOT was consistent with two additional findings: more patients achieved surgical resection with FLOT compared with ECF/ECX, and, in patients undergoing resection, there was a greater proportion of postoperative stage ypT0, ypT1, or ypT2 tumours with FLOT than with ECF/ECX. For patients who had resectional surgery, the frequency of microscopically complete resections was similar in both treatment groups. Because more patients in the ECF/ECX group than in the FLOT group were found to be irresectable at surgery, we believe that the study surgeons were very selective in performing resectional surgery and this might have led to similar rates of microscopically complete resection in the resected group. The increased frequency of pathological regression with FLOT seemed to lead to fewer patients having progressive disease during therapy or irresectability at surgery than with ECF/ECX. Both factors are usually associated with incurability and can be more closely linked to survival than pathological regression itself. This represents a possible mechanism by which protocols with improved efficiency can have an impact on survival, in addition to rationally assumed better control of systemic microscopic disease.

We observed substantial differences in histopathological regression between diffuse and intestinal type tumours. Patients with intestinal type tumours derived the highest benefit from FLOT compared with ECF/ECX. In diffuse type tumours, the proportion of patients who achieved pathological complete regression with either treatment was less than 3%, and the proportion who achieved TRG1a or TRG1b was similar between groups. The finding that docetaxel-based FLOT appears to have a greater effect in the intestinal type histology compared with the diffuse type histology is interesting. If confirmed, this could guide a more individualised therapeutic approach dependent on histological type.

However, limitations regarding Lauren's classification in the preoperative therapy setting exist. Lauren's classification type is determined based on pre-therapeutic samples. As a result, many patients are considered not classifiable according to Lauren's classification based on the small biopsies available at baseline.

Some points and limitations of this study deserve discussion. The proportions of patients with gastric and gastro-oesophageal junction primary tumours were not balanced between the FLOT and ECF/ECX treatment groups. However, we do not believe that this discrepancy had an effect on outcomes. FLOT treatment was associated with higher proportions of patients with pathological complete regression and TRG1a and TRG1b than ECF/ECX in patients with both types of tumours and the proportions of patients who had a resection and had an R0 resection were similar in patients with gastric and gastro-oesophageal junction primary tumours. The proportion of patients who had clinical node positivity was high (79%), and there were no protocol-specific imaging criteria to define lymph node positivity. We believe that in clinical studies and in routine care, nodal status tends to be overstaged. We believe this overstaging did not cause significant bias because the nodal status was similar between treatment groups. Pathological regression was assessed by only one central pathologist. However, complete regression results were in line with the local pathology results.

There are remarkable disparities in the perioperative chemotherapy regimens for gastric and gastro-oesophageal junction cancer among different countries. Some experts recommend perioperative fluorouracil and oxaliplatin without a third drug because of potential toxicity, and because they are concerned that perioperative taxane treatment will leave few options for second-line therapy. However, preoperative use of fluorouracil and platinum-doublet regimens has been consistently associated with a pathological complete regression in only 2–3% of patients,[14,16,23] which, in our opinion, might represent undertreatment in a patient who would tolerate the addition of docetaxel. In the perioperative setting, the risk–benefit ratio of intense combinations can be more favourable than in the metastatic setting, because patients with localised disease are usually fitter and have a chance of long-term survival after a limited therapy period. In terms of non-surgical adverse events, both ECF/ECX and FLOT were well tolerated and the incidences of adverse events were in line with previous reports in the perioperative setting.[2,7,8,11] In terms of subsequent therapy, patients who have early recurrence after FLOT can be offered irinotecan and fluorouracil, an effective chemotherapy without taxanes or platinum.[25]

In conclusion, the docetaxel-based triplet FLOT significantly increased the proportion of patients achieving pathological complete regression compared with ECF/ECX. This effect was probably attributable to a more pronounced activity of FLOT in tumours with intestinal histology. Over the past 10 years, based on phase 2 studies and the personal experience of physicians, FLOT has become one of the standard protocols for perioperative therapy of gastric and gastro-oesophageal junction cancer in Germany. In the international context, FLOT could represent an option for patients with intestinal type tumours, for whom the achievement of a pathological regression is considered to be of particular importance. Otherwise, the final results of the phase 3 part should show whether the favourable pathological regression with FLOT translates into better survival outcomes than with ECF/ECX. The observation that histopathological regression was closely related to Lauren's classification stresses the necessity to consider histology in prospective trials and when interpreting available data or comparing data across trials.

Contributors

S-EA-B had the original idea, designed the study, and was responsible for protocol development. All authors except CP, SM, MSc, MSi, and AT recruited patients into the study and collected data. All authors contributed to data interpretation. S-EA-B wrote the report, with revisions from all the other authors. S-EA-B did the literature search. S-EA-B and CP developed the figures. CP was responsible for project management.

Declaration of interests

S-EA-B is an adviser for Merck, Roche, Celgene, Lilly, and Nordic Pharma; has received speaker's fees fromRoche, Celgene, Lilly, and Nordic Pharma; and has received research grants from Sanofi, Merck, Roche, Celgene, Vifor, Medac, Hospira, and Lilly. GMH has served as an adviser for Sanofi, Roche, Taiho, Lilly, and Pfizer; and has received travel grants from Ipsen and Celgene. RDH has received research grants from Sanofi. SL has served as an adviser for Sanofi. HS has received research grants from Sanofi. JT is an adviser for Roche, Lilly, and Nordic Pharma; and has received speaker's fees from Roche and Lilly. WS has served as an adviser for Aicuris, Amgen, Apceth, AstraZeneca, Indivumed, Merck Serono, and Roche; has received speaker's fees from Abbott, Falk Foundation, GSB, Lilly, MCI, Medcongress, Pfizer, Sanofi-Aventis, Siemens Healthcare, Merck Serono, and Roche; and has received honoraria from Deutschlandfunk, Deutsches Ärzteblatt, Elsevier Verlag, Springer Verlag, Westdeutscher Rundfunk, and Zweites Deutsches Fernsehen. MP has received research grants from Amgen, Baxalta, Celgene, Lilly, MCI, Merck Serono, Roche, and Shire. MSc has served as an adviser for AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, Lilly, Novartis, and Roche; has received speaker's fees from Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, and Novartis; and has received research grants from Boehringer Ingelheim, Bristol Myers-Squibb, and Novartis. MSi is an employee of Sanofi. All other authors declare no competing interests.

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