



# Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial

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## Summary

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**Background** Docetaxel-based chemotherapy is effective in metastatic gastric and gastro-oesophageal junction adenocarcinoma. This study reports on the safety and efficacy of the docetaxel-based triplet FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) as a perioperative therapy for patients with locally advanced, resectable tumours.

**Methods** In this controlled, open-label, phase 2/3 trial, we randomly assigned 716 patients with histologically-confirmed advanced clinical stage cT2 or higher or nodal positive stage (cN+), or both, resectable tumours, with no evidence of distant metastases, via central interactive web-based-response system, to receive either three pre-operative and three postoperative 3-week cycles of 50 mg/m<sup>2</sup> epirubicin and 60 mg/m<sup>2</sup> cisplatin on day 1 plus either 200 mg/m<sup>2</sup> fluorouracil as continuous intravenous infusion or 1250 mg/m<sup>2</sup> capecitabine orally on days 1 to 21 (ECF/ECX; control group) or four preoperative and four postoperative 2-week cycles of 50 mg/m<sup>2</sup> docetaxel, 85 mg/m<sup>2</sup> oxaliplatin, 200 mg/m<sup>2</sup> leucovorin and 2600 mg/m<sup>2</sup> fluorouracil as 24-h infusion on day 1 (FLOT; experimental group). The primary outcome of the trial was overall survival (superiority) analysed in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT01216644.

**Findings** Between Aug 8, 2010, and Feb 10, 2015, 716 patients were randomly assigned to treatment in 38 German hospitals or with practice-based oncologists. 360 patients were assigned to ECF/ECX and 356 patients to FLOT. Overall survival was increased in the FLOT group compared with the ECF/ECX group (hazard ratio [HR] 0.77; 95% confidence interval [CI; 0.63 to 0.94]; median overall survival, 50 months [38.33 to not reached] vs 35 months [27.35 to 46.26]). The number of patients with related serious adverse events (including those occurring during hospital stay for surgery) was similar in the two groups (96 [27%] in the ECF/ECX group vs 97 [27%] in the FLOT group), as was the number of toxic deaths (two [ $<1\%$ ] in both groups). Hospitalisation for toxicity occurred in 94 patients (26%) in the ECF/ECX group and 89 patients (25%) in the FLOT group.

**Interpretation** In locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma, perioperative FLOT improved overall survival compared with perioperative ECF/ECX.

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## Introduction

The prognosis of patients with gastric and gastro-oesophageal junction adenocarcinoma is poor.<sup>1</sup> Compared with surgery alone, several therapeutic approaches including perioperative chemotherapy or adjuvant or neoadjuvant chemoradiation improve survival.<sup>2–5</sup> The

first and largest study to show a survival benefit of perioperative chemotherapy was the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial.<sup>2</sup> 503 patients with locally advanced, resectable oesophagogastric adenocarcinoma were treated with either three cycles of epirubicin, cisplatin, and

## Research in context

### Evidence before this study

For this manuscript 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 Jan 1 to May 25, 2018. For the PubMed search, we used full-text search terms for “gastric cancer”, “oesophageal cancer” or “gastro-oesophageal junction cancer” in conjunction with “neoadjuvant treatment” or “perioperative treatment” as well as “resectable” or “operable stage” or “operable patients”. We limited our discussion to trials and reports that we found relevant to the setting of our trial as well as our population, and results.

The prognosis of patients with gastric cancer was poor in the more advanced tumours. Perioperative chemotherapy for gastric and gastro-oesophageal junction adenocarcinoma was established and shown to improve survival in two landmark clinical trials: the MAGIC trial using three 3-week cycles of ECF (epirubicin and cisplatin plus fluorouracil) followed by surgery followed by three additional ECF cycles showing significant improvement in 5-year overall survival (36% vs 23%) and the French FNCLCC/FFCD 9703-3 study, in which patients received 2–3 cycles of cisplatin with fluorouracil before and after surgery or surgery alone, resulting in a significant and similar improvement of 5-year overall survival (38% vs 24%). However, despite these advances, the outcome for patients with advanced

gastric or gastric and gastro-oesophageal junction adenocarcinoma remained unsatisfactory. At that time, docetaxel had proven efficacy in metastatic gastric cancer, both in first-line and second-line settings. Our group previously demonstrated the activity and safety of the docetaxel-based triple combination FLOT, consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel, administered every 2 weeks in the treatment of patients with metastatic gastric cancer and found FLOT induced pathological complete regression of up to 17% in phase 2 and retrospective studies.

### Added value of this study

To our knowledge, this is the first trial to show significant improvement over the available standard of care ECF in the treatment of patients with locally advanced, potentially resectable gastric and gastro-oesophageal junction adenocarcinoma. The study showed that perioperative FLOT significantly improved overall survival as compared with perioperative ECF or ECX (epirubicin and cisplatin plus either fluorouracil or capecitabine).

### Implications of all the available evidence

The study expands the available options for the treatment of locally advanced, resectable gastric and gastro-oesophageal adenocarcinoma.

fluorouracil (ECF) administered before and after surgery or surgery alone. The chemotherapy arm showed a significant improvement in overall survival (5-year survival rates, 36% vs 23%) compared with surgery alone. However, despite these advances, the outcome for patients with gastric or gastro-oesophageal junction adenocarcinoma remains unsatisfactory. Subsequent trials aiming to achieve a substantial improvement over the established regimens failed.<sup>6–9</sup>

The cytotoxic drug docetaxel has shown efficacy in the metastatic settings, both in first-line (docetaxel, cisplatin, and fluorouracil [DCF] administered every 3 weeks)<sup>10</sup> and second-line (docetaxel monotherapy) therapy.<sup>11</sup> However, the parent DCF regimen was associated with high toxicity and this prompted us to develop a modified regimen delivered once every 2 weeks using oxaliplatin instead of cisplatin to reduce the toxicity. In several phase 2 studies, we evaluated this new combination consisting of fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for metastatic<sup>12–14</sup> and locally advanced<sup>15,16</sup> gastric and gastro-oesophageal junction adenocarcinoma, and showed that FLOT was more tolerable than the parent DCF regimen and that it induced more tumour responses in locally advanced, resectable tumours than other regimens, including the anthracycline-based triplets.<sup>15–17</sup> This prompted us to evaluate FLOT in a randomised, phase 2/3 trial, comparing perioperative epirubicin and cisplatin plus either fluorouracil or capecitabine

(ECF/ ECX) with perioperative FLOT. The results of the phase 2 study (comprising the first 300 patients of the total population) were published in 2017<sup>18</sup> and showed that FLOT was superior to ECF/ECX in terms of complete pathological regression (15% vs 6%;  $p=0.02$ ). In the phase 3 trial portion reported here, we aimed to assess overall survival in an expanded population.

## Methods

### Study design and participants

The FLOT4-Arbeitsgemeinschaft Internistische Onkologie (AIO) trial was an investigator-initiated multicentre (hospitals and practice-based oncologists), randomised, unmasked, controlled trial. The trial was overseen by a steering committee (web appendix). The trial was done in accordance with the principles of the Declaration of Helsinki. All versions of the trial protocol were approved by the responsible ethic committees. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report to the protocol. Study management and coordination were done by the Institute of Clinical Cancer Research. Data management and on-site monitoring were done by independent institutions, which are Trium Analysis Online, Munich, Germany and MCA, Berlin, Germany, respectively.

Eligible patients had histologically confirmed gastric or gastro-oesophageal junction adenocarcinoma of a clinical

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stage cT2 or higher nodal positive stage (cN+), or both and no clinical evidence of distant metastases according to the 7th Edition of the International Union against Cancer tumour–node–metastasis classification. Adenocarcinomas of the gastro-oesophageal junction were classified according to Siewert.<sup>19</sup> Complete eligibility criteria are listed in the web appendix. We assessed clinical stage by physical examination, oesophagogastroduodenoscopy, endoscopic ultrasound, and CT or MRI of the chest, abdomen, and pelvis. Diagnostic laparoscopy was recommended but was not mandatory in accordance with standard of care in Germany.<sup>20</sup> All patients gave written informed consent.

## Randomisation

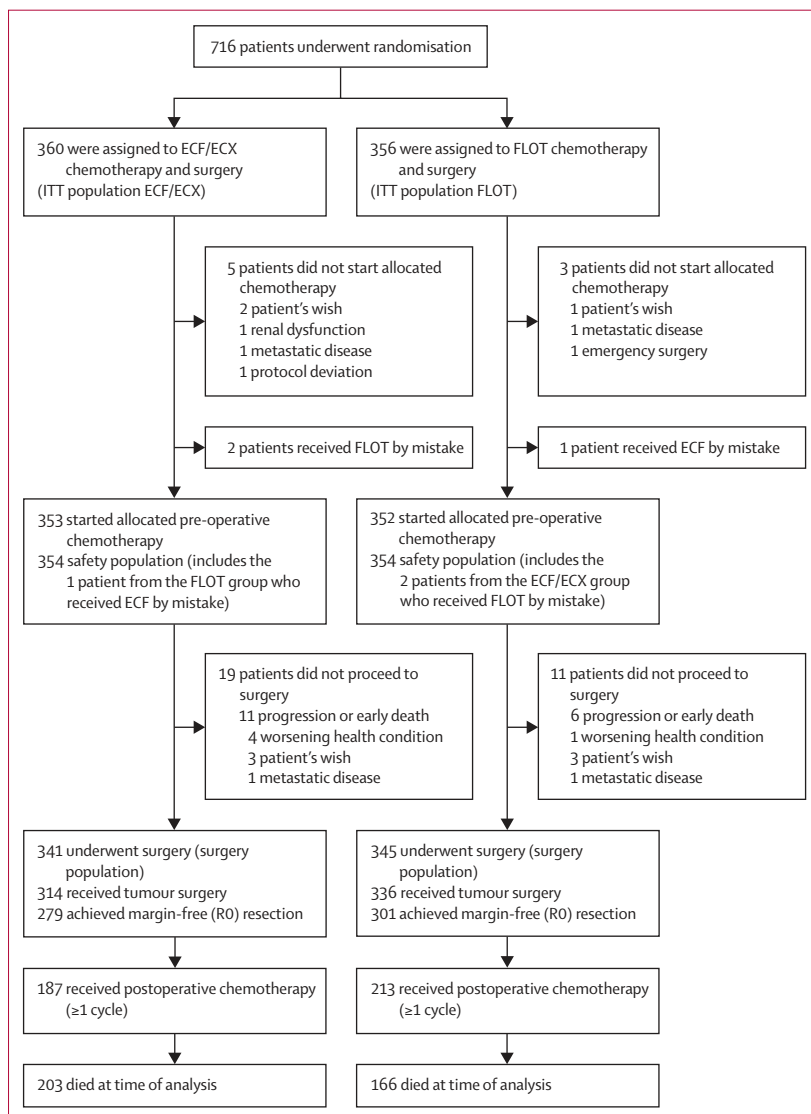
Patients were centrally randomised 1:1 to surgical resection with either perioperative ECF/ECX or perioperative FLOT using an interactive web-response system (IWRS) based on a sequence generated with permuted blocks stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs 2), location of primary tumour (GEJ Type I vs GEJ type II/III vs. gastric), age (<60 vs 60–69 vs ≥70 years), and suspected lymph node involvement (N+ vs N-). Patients were enrolled by authorised individuals who requested randomisation using IWRS integrated in the electronic Case Report Forms. Actual assignment to trial groups took place on the server of the independent data management providers (Irium Analysis Online, Munich, Germany) by means of a validated SAS program, which underlies strict access control. The randomisation system allocated every patient a unique identification number and sent a message that included allocation result to the investigator. The study was open-label and no masking was required.

## Procedures

ECF/ECX was administered for three preoperative cycles followed by three postoperative cycles. Each 3-week cycle of ECF/ECX consisted of epirubicin 50 mg/m<sup>2</sup> on day 1, cisplatin 60 mg/m<sup>2</sup> on day 1, and fluorouracil 200 mg/m<sup>2</sup> as continuous intravenous infusion on days 1 to 21. Fluorouracil could be replaced by capecitabine 1250 mg/m<sup>2</sup> administered orally on days 1 to 21 (investigator's choice). FLOT was administered for four preoperative cycles followed by four postoperative cycles. Each 2-week cycle of FLOT consisted of docetaxel 50 mg/m<sup>2</sup> on day 1, oxaliplatin 85 mg/m<sup>2</sup> on day 1, leucovorin 200 mg/m<sup>2</sup> on day 1, and 5-FU 2600 mg/m<sup>2</sup> as 24-h infusion on day 1. Dose modification schedule and the recommended supportive therapy are given in the web appendix. Granulocyte colony stimulating factors (GCSF) were not used as primary prophylaxis (see appendix). Therapy was stopped prematurely for unacceptable toxicity, disease progression, death, or at the patient's request.

Surgery was scheduled for 4 weeks after the last dose of preoperative chemotherapy. The study protocol required transthoracic esophagectomy (Ivor-Lewis procedure) with resection of the proximal stomach and 2-field (mediastinal and abdominal) lymphadenectomy for type 1 gastro-oesophageal junction cancers and gastrectomy with transhiatal distal oesophagectomy plus D2 lymphadenectomy for types 2 and 3 gastro-oesophageal junction cancers. For gastric tumors, total or subtotal distal gastrectomy with D2 lymphadenectomy was performed, which represents standard of care in Germany.<sup>20</sup> We selected centres with experienced surgery departments (or established collaboration with such departments). The surgery reports were reviewed centrally by an experienced surgeon (TG).

Patients were assessed according to medical history, physical examination, weight, ECOG performance status, complete blood count, and blood chemical tests



**Figure 1: Trial profile**

Of the 716 patients who underwent randomisation, 360 were assigned to the ECF/ECX chemotherapy-surgery group and 356 to the FLOT chemotherapy-surgery group. All randomised patients were included in the intention-to-treat population. All patients who received at least one cycle of ECF/ECX or FLOT chemotherapy were included in the safety population. Patients who had surgery were included in the surgery population. ECF/ECX=epirubicin and cisplatin plus either fluorouracil or capecitabine. FLOT=fluorouracil plus leucovorin, oxaliplatin and docetaxel. ITT=intention-to-treat.

	ECF/ECX (n=360)	FLOT (n=356)
<b>Age (years)</b>		
Median	62 (52–69)	62 (54–69)
<60	160 (44%)	155 (44%)
60–69	113 (31%)	116 (33%)
≥70	87 (24%)	85 (24%)
<b>Sex</b>		
Male	265 (74%)	268 (75%)
Female	95 (26%)	88 (25%)
<b>ECOG</b>		
0	254 (71%)	246 (69%)
1	103 (29%)	109 (31%)
2	3 (1%)	1 (<1%)
<b>Location</b>		
GEJ Siewert type 1*	85 (24%)	80 (23%)
GEJ Siewert type 2 or 3	115 (32%)	118 (33%)
Stomach	160 (44%)	158 (44%)
<b>cT-stage†</b>		
T1	2 (1%)	3 (1%)
T2	59 (16%)	49 (14%)
T3	253 (70%)	267 (75%)
T4	33 (9%)	28 (8%)
unclear	13 (4%)	9 (3%)
<b>cN-stage‡</b>		
N–	70 (19%)	77 (22%)
N+	290 (81%)	279 (78%)
<b>Barrett's carcinoma‡</b>		
Yes	54 (15%)	53 (15%)
No	297 (83)	301 (85%)
Unclear or unknown	4 (1%)	2 (1%)
Missing	5 (1%)	0 (0)
<b>Lauren's type</b>		
Diffuse	96 (27%)	95 (27%)
Intestinal or mixed	163 (45%)	159 (45%)
Not evaluable according to Lauren	72 (20%)	70 (20%)
Missing	29 (8%)	32 (9%)

(Table 1 continues in next column)

at baseline and before the start of every cycle. Restaging by means of computed CT or MRI and endoscopy was done before surgery. Follow-up included CT or MRI every three months until disease progression, relapse, or death. Disease progression could be a progression of the primary or the lymph nodes or the occurrence of new lesions before surgery, or the discovery of metastatic disease during surgery (if this was not retrospectively judged as pre-existent by the investigator).

## Outcomes

The primary outcome of the phase 2 study was the rate of pathological complete tumour regression according to Becker classification.<sup>17</sup> The primary outcome of the phase 3 was initially disease-free survival but was changed to overall survival upon a request of the independent

	ECF/ECX (n=360)	FLOT (n=356)
(Continued from previous column)		
<b>Signet cells§</b>		
Yes	101 (28%)	100 (28%)
No	234 (65%)	245 (69%)
Missing	25 (7%)	11 (3%)
<b>Grading according to WHO¶</b>		
G1	21 (6%)	12 (3%)
G2	131 (36%)	123 (35%)
G2–3	10 (3%)	12 (3%)
G3	177 (49%)	177 (50%)
Missing	21 (6%)	32 (9%)

Data are median (IQR) or n (%). Percentages might not add up to 100 because of rounding. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil, leucovorin, oxaliplatin, and docetaxel. ECOG=Eastern Cooperative Oncology Group. GEJ=gastro-oesophageal junction. cN+=nodal positive. cN–=nodal negative. \*Adenocarcinomas of the gastro-oesophageal junction were classified according to the Siewert classification as tumours having their centre 5 cm proximal or distal of the anatomical cardia. Siewert type 1 tumours are described as adenocarcinoma of the distal oesophagus, which usually arises from an area with specialised intestinal metaplasia of the oesophagus (ie, Barrett's oesophagus) and which might infiltrate the oesophagogastric junction from above.<sup>18</sup> Note, Siewert type 1 tumours might not involve the junction and might have been classified as oesophageal adenocarcinomas in other studies. †Clinical tumour stage and clinical nodal (cN) stage were assessed by endoscopic ultrasound and CT or MRI and classified according to the seventh version of the International Union against Cancer tumour–node–metastasis classification. ‡Barrett's carcinoma was defined as the presence of Barrett's mucosa in tumours of the gastro-oesophageal junction as assessed by either baseline endoscopy or pathological examination. Stomach tumours were automatically regarded non-Barrett. §Defined as the presence of any signet cells. ¶WHO performance status scores are on a scale of 0 to 5, with lower numbers indicating better performance status; 0 indicates fully active and 1 unable to carry out heavy physical work.

**Table 1: Baseline characteristics of the intention-to-treat population according to treatment group**

scientific committee of the German Cancer Aid. Overall survival was defined as time from randomisation to death. Secondary outcomes included margin-free-(R0) resection rate; disease-free survival, defined as time from randomisation to disease progression, relapse, or death; surgical morbidity and mortality; and adverse events according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

## Statistical analysis

Here, we describe the current sample size after overall survival was amended to the protocol as the primary outcome. We estimated the median overall survival in the ECF/ECX group to be 25 months, based on the results of the MAGIC trial.<sup>2</sup> The calculated sample size was 658 patients, assuming an improvement in overall survival by FLOT at a hazard ratio (HR) of 0.76 (80% power for a two-sided log-rank test at an  $\alpha$  level of 0.05), a 4 years enrolment time, a 6 years total follow-up time, and allowing for a 15% dropout rate. We later increased the patient number to 714 to allow for a dropout rate of up to 24% (based on theoretical assumptions). There were no observations indicative of

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See Online for appendix

	ECF/ECX (n=360)	FLOT (n=356)
Proceeded to surgery	341 (95%)	345 (97%)
Received tumour surgery	314 (87%)	336 (94%)
Achieved margin-free (R0) resection	279 (78%)	301 (85%)
Type of surgery		
Transthoracic oesophagectomy	98 (27%)	109 (31%)
Gastrectomy with or without transhiatal oesophagectomy	200 (56%)	208 (58%)
Multivisceral resection	10 (3%)	15 (4%)
Other tumour surgery	6 (2%)	4 (1%)
Palliative (non-curative) resection	6 (2%)	0 (0)
Non-resectional surgery	21 (6%)	9 (3%)
No surgery	19 (5%)	11 (3%)
Median number of lymph nodes removed*	25.0 (19–33)	24.0 (18–32)
Type of lymphadenectomy		
2-Field	106 (29%)	113 (32%)
D2	192 (53%)	204 (57%)
3-Field	2 (1%)	1 (<1%)
D3	5 (1%)	10 (3%)
D1	7 (2%)	5 (1%)
Missing	7 (2%)	3 (1%)
Not applicable or D0†	41 (11%)	20 (6%)
Tumour stage (ypT)		
≤T1	53 (15%)	88 (25%)
T2	44 (12%)	44 (12%)
T3	175 (49%)	165 (46%)
T4	47 (13%)	37 (10%)
Not applicable‡	41 (11%)	22 (6%)
Nodal status (ypN)		
N0	146 (41%)	174 (49%)
N1	44 (12%)	55 (16%)
N2	54 (15%)	47 (13%)
N3	73 (20%)	57 (16%)
Not applicable‡	43 (12%)	23 (7%)

Data are median (IQR) or n (%). Percentages may not add up to 100 because of rounding. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil plus leucovorin, oxaliplatin, and docetaxel. ypT=postoperative T-stage following preoperative chemotherapy. ypN=postoperative N-stage following preoperative chemotherapy. \*Numbers were calculated in the group of patients who had tumour surgery. †Includes patients who could not be staged due to no operation, palliative surgery, or others.

**Table 2: Surgical and pathology results in the intention-to-treat population according to treatment group**

a dropout rate that is higher than usual. A co-primary endpoint was non-inferiority, tested if superiority tests failed to reach significance according to Freidlin and colleagues.<sup>21</sup> We analysed disease-free and overall survival by the Kaplan-Meier method in the intention-to-treat (ITT) population (figure 1). A prespecified sensitivity analysis included overall survival adjusted for the stratification factors using a Cox proportional-hazards model, for which proportional hazard assumptions were checked for violations using standard

graphical methods. The safety population comprised all patients who received at least one cycle of chemotherapy, analysed as treated (figure 1). For each group, we calculated and compared the incidence of adverse events and the incidence of serious adverse events between the groups. We did a subgroup analysis to assess whether the relative effect from FLOT varies according to baseline characteristics, and we evaluated the heterogeneity of the treatment effect by an interaction test and presented it using a forest plot. We prespecified the subgroup analysis in the study analysis plan. We tested time-to-event comparisons with the log-rank model. We compared all other groups using the chi-squared test. All p values were 2-sided. We did the analysis using SAS software program version 9.3.

**Role of the funding source**

The independent scientific committee of the German Cancer Aid reviewed and approved the study protocols. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report and had no access to the raw data. S-EAB, CP, and TG had access to the raw data. The corresponding author had final responsibility for the decision to submit for publication. All authors approved the final version of the manuscript submitted for publication.

**Results**

The results of the phase 2 study were focused on pathological regression and were published elsewhere.<sup>18</sup> This report discusses the results of the phase 3 study.

Between Aug 8, 2010, and Feb 10, 2015, 716 patients were randomly assigned to treatment in 38 German cancer sites (figure 1). Follow-up of the last patient ended March 7, 2017. Baseline characteristics were similar between the groups (table 1). Diagnostic laparoscopy at baseline was done in 147 (41%) patients in the ECF/ECX group and 139 (39%) patients in the FLOT group.

353 (98%) of 360 patients started allocated chemotherapy in the ECF/ECX group and 352 (99%) of 356 in the FLOT group. 326 (91%) patients in the ECF/ECX group and 320 (90%) patients in the FLOT group completed all cycles of allocated preoperative chemotherapy. In the ECF/ECX group, 240 (67%) of 360 patients received capecitabine as the fluoropyrimidine (ECX). 186 (52%) of 360 patients in the ECF/ECX group and 213 (60%) of 356 patients in the FLOT group started allocated postoperative chemotherapy. Of all patients randomised, 132 (37%) patients in the ECF/ECX group and 162 (46%) patients in the FLOT group completed all allocated cycles. The cumulative doses and dose modifications are in the web appendix. Dose delays (>7 days) occurred in 31 (2%) of 1515 cycles in the ECF/ECX group and 56 (3%) of 2101 cycles in the FLOT group. GCSFs were administered with the first cycle in 22 patients (6%) in the ECF/ECX group and 17 patients (5%) in the FLOT group. 77 patients (21%) in the ECF/ECX group and 121 (34%) in the FLOT group received GCSFs at any

time-point. The most common reasons for discontinuing chemotherapy were disease progression, lack of efficacy or early death in 74 (21%) of 360 patients in the ECF/ECX group and 46 (13%) of 356 patients in the FLOT group followed by patients' request (in 62 [17%] in the ECF/ECX group and 59 [17%] of patients in the FLOT group), and toxicity (47 [13%] and 35 [10%] of patients).

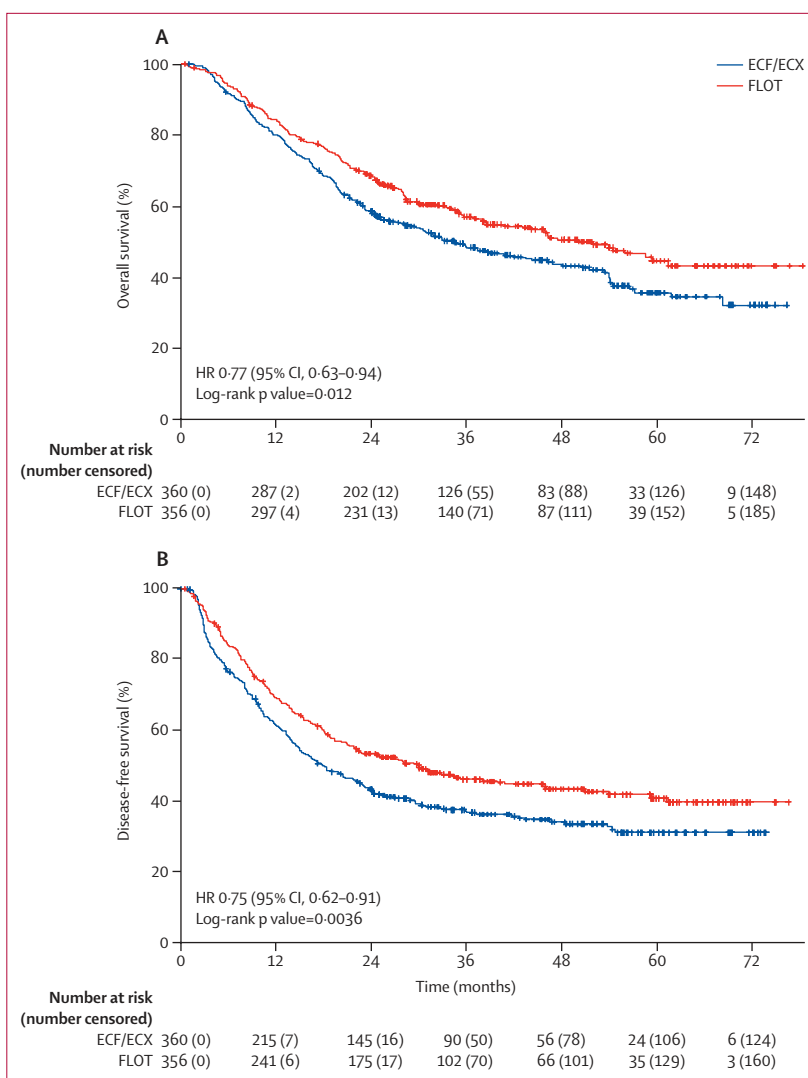
Similar rates of patients proceeded to surgery in the ECF/ECX group and FLOT group (table 2; 341 [95%] of 360 patients vs 345 [97%] of 356 patients). However, in the FLOT group, significantly more patients received tumour surgery (336 [94%] vs 314 [87%];  $p=0.001$ ). Reasons for not proceeding to surgery are in figure 1. Median time between start of chemotherapy and surgery was 13.1 weeks in the ECF/ECX group and 11.1 weeks in the FLOT group.

Pathological findings were based on local pathology results (table 2). While baseline cT and cN stages were similarly distributed among the groups, a higher proportion of stage ypT1 tumours were in the FLOT group than in the ECF/ECX group (88 [25%] of 356 patients vs 53 [15%] of 360 patients;  $p=0.0008$ ). A higher proportion of tumours were stage ypN0 in the FLOT group than in the ECF/ECX group (174 [49%] of 356 patients vs 146 of [41%] 360 patients;  $p=0.025$ ). In the ITT population, more patients achieved margin-free-(R0) resection in the FLOT group than in the ECF/ECX group (301 [85%] vs 279 [78%];  $p=0.0162$ ).

The primary outcome, median overall survival, was 35 months (95% CI 27.35 to 46.26) in the ECF/ECX group and 50 months (38.33 to not reached) in the FLOT group (HR 0.77; 0.63 to 0.94;  $p=0.012$ ; figure 2). The estimated overall survival at 2, 3, and 5 years were 59% (95% CI 53 to 64), 48% (43 to 54), and 36% (30 to 42) in the ECF/ECX group, as compared with 68% (63 to 73), 57% (52 to 62), and 45% (38 to 51) in the FLOT group.

Chemotherapy-associated toxicity was analysed in the safety population comprising 354 patients in each group (figure 1). We observed significantly more grade 3 or 4 nausea (55 [16%] in the ECF/ECX group vs 26 [7%] in the FLOT group), vomiting (27 [8%] vs 7 [2%]), thromboembolic events (21 [6%] vs 9 [3%]), and anaemia (20 [6%] vs 9 [3%]) in the ECF/ECX group and more grade 3 or 4 infections (30 [9%] vs 63 [18%]), neutropenia (139 [39%] vs 181 [51%]), diarrhoea (13 [4%] vs 34 [10%]), and neuropathy (7 [2%] vs 24 [7%]) in the FLOT group (table 3). Febrile neutropenia was observed in two patients (1% in the ECF/ECX group and seven patients (2% in the FLOT group). The number of patients with serious adverse events related to treatment (including those occurring during hospital stay for surgery) was similar in the two groups (96 [27%] in the ECF/ECX group vs 97 [27%] in the FLOT group), as was the number of toxic deaths (two [ $<1\%$ ] in both groups). Hospitalisation for toxicity occurred in 94 patients (26%) in the ECF/ECX group and 89 patients (25%) in the FLOT group.

The incidence of postoperative complications, as assessed in the surgery population, was similar in both



**Figure 2: Kaplan-Meier estimates of overall survival (A) and disease-free survival (B)**

(A) Overall survival in the intention-to-treat population in the ECF/ECX group versus the FLOT group.

(B) Disease-free survival in the intention-to-treat population in the ECF/ECX group versus the FLOT group.

(ECF/ECX=epirubicin and cisplatin plus either fluorouracil or capecitabine. FLOT=fluorouracil plus leucovorin, oxaliplatin and docetaxel. HR=hazard ratio. CI=confidence interval.

groups (170 [50%] of 341 patients in the ECF/ECX group and 175 [51%] in 345 patients in the FLOT group). The median duration of hospital stay was similar in the two groups (16 days in the ECF/ECX group and 15 days in the FLOT group) as were the number of re-operations (37 [11%] and 34 [10%], respectively) and deaths within 30 days (ten [3%] and six [2%], respectively). Deaths within 90 days were 26 patients (8%) in the ECF/ECX group and 16 patients (5%) in the FLOT group.

The median follow-up for surviving patients was 43 months in both groups and 350 (97%) of 360 patients in the ECF/ECX group and 343 (96%) of 356 patients in the FLOT group had died or were followed for more than 2 years. At the time of the analysis, 203 (56%) patients in the ECF/ECX group and 166 (47%) patients in the FLOT

	ECF/ECX (n=354)		FLOT (n=354)		Difference in grade 3 or 4 events (p value)
	Grade 1 or 2	Grade 3 or 4	Grade 1 or 2	Grade 3 or 4	
Diarrhoea	103 (29%)	13 (4%)	182 (52%)	34 (10%)	0.0016
Vomiting	102 (29%)	27 (8%)	113 (32%)	7 (2%)	<0.001
Nausea	215 (61%)	55 (16%)	211 (60%)	26 (7%)	<0.001
Constipation	86 (24%)	1 (<1%)	75 (21%)	2 (1%)	0.56
Stomatitis or mucositis	107 (30%)	10 (3%)	99 (28%)	5 (1%)	0.19
Leukopenia	175 (49%)	75 (21%)	180 (51%)	94 (27%)	0.098
Neutropenia	93 (26%)	139 (39%)	84 (24%)	181 (51%)	0.0017
Anaemia	282 (80%)	20 (6%)	283 (80%)	9 (3%)	0.036
Thrombocytopenia	123 (35%)	11 (3%)	137 (39%)	7 (2%)	0.34
Serum AST	41 (12%)	1 (<1%)	116 (33%)	3 (1%)	0.31
Serum ALT	55 (16%)	1 (<1%)	127 (36%)	8 (2%)	0.019
Fever	29 (8%)	2 (1%)	77 (22%)	4 (1%)	0.41
Peripheral neuropathy	120 (34%)	7 (2%)	228 (64%)	24 (7%)	0.0018
Pain	171 (48%)	14 (4%)	166 (47%)	21 (6%)	0.23
Alopecia*	147 (42%)	74 (21%)	122 (35%)	98 (28%)	NA
Renal	99 (28%)	1 (<1%)	38 (11%)	0 (0)	0.32
Infections	62 (18%)	30 (9%)	61 (17%)	63 (18%)	<0.001
Thromboembolic	31 (9%)	21 (6%)	13 (4%)	9 (3%)	0.025
Toxic death†	..	2 (<1%)	..	2 (<1%)	1.0

Except for toxic deaths, adverse events are displayed when they were observed in 20% or more patients at grade 1 or 2 or 5% or more patients at grade 3 or 4. ECF=epirubicin, cisplatin, and fluorouracil. ECX=epirubicin, cisplatin, and capecitabine. FLOT=fluorouracil plus leucovorin, oxaliplatin, and docetaxel. AST=aspartate aminotransferase. ALT=alanine-aminotransferase. NA=not applicable. \*The highest grade of alopecia was grade 2, which is listed in the grade 3 or 4 column. †Toxic death was defined as a chemotherapy-related toxicity resulting in death.

**Table 3: Potentially chemotherapy-associated adverse events (whether related or not) assessed in the safety population according to treatment group**

group had died. 230 (64%) patients in the ECF/ECX group and 193 (54%) patients in the FLOT group had disease progression, relapse or death.

Median disease-free survival was 18 months in the ECF/ECX group and 30 months in the FLOT group (HR, 0.75; 95% CI, 0.62–0.91; p=0.0036) (figure 2). The HR for overall survival adjusted by the stratification factors in the Cox proportional-hazards model was similar and was 0.76 (95% CI 0.62 to 0.94; p=0.0093). Overall survival in the per-protocol population, comprising all eligible patients who received at least one cycle of chemotherapy, analysed as treated, supported the intention-to-treat analysis (appendix). The relative treatment effect of FLOT was consistent across subgroups, specifically with relation to age, anatomical site, histology, and clinical stage (figure 3). All tests of interaction were negative (figure 3). A post-hoc Kaplan-Meier analysis for the gastric and gastro-oesophageal adenocarcinoma and for the nodal negative (cN-) and nodal positive (cN+) subgroups is given in the web appendix.

### Discussion

In this trial, overall survival was longer in patients with gastric or gastro-oesophageal junction adenocarcinoma

who received perioperative chemotherapy with FLOT compared with those who received ECF/ECX. Median overall survival increased by 15 months and the estimated 2-year, 3-year, and 5-year survival rates by 9%, and the benefit in survival is clinically meaningful. In addition, FLOT significantly improved other clinically relevant endpoints such as resectability and disease-free survival.

The control group (ECF/ECX) in our study did not underperform based on results of previous studies. In the reference trial MAGIC,<sup>2</sup> perioperative ECF was associated with a median overall survival of 25 months, while median survival in the ECF/ECX group in the FLOT4 trial amounted to 35 months. The more recent UK Medical Research Council ST03 trial<sup>7</sup> compared perioperative ECX with ECX plus bevacizumab for patients with locally advanced, resectable gastric, oesophageal and gastro-oesophageal junction adenocarcinoma. The study reported 3-year survival of 50% with chemotherapy alone and 48% with chemotherapy plus bevacizumab. These numbers were consistent with the 3-year survival (48%) observed in the ECF/ECX group in the present study.

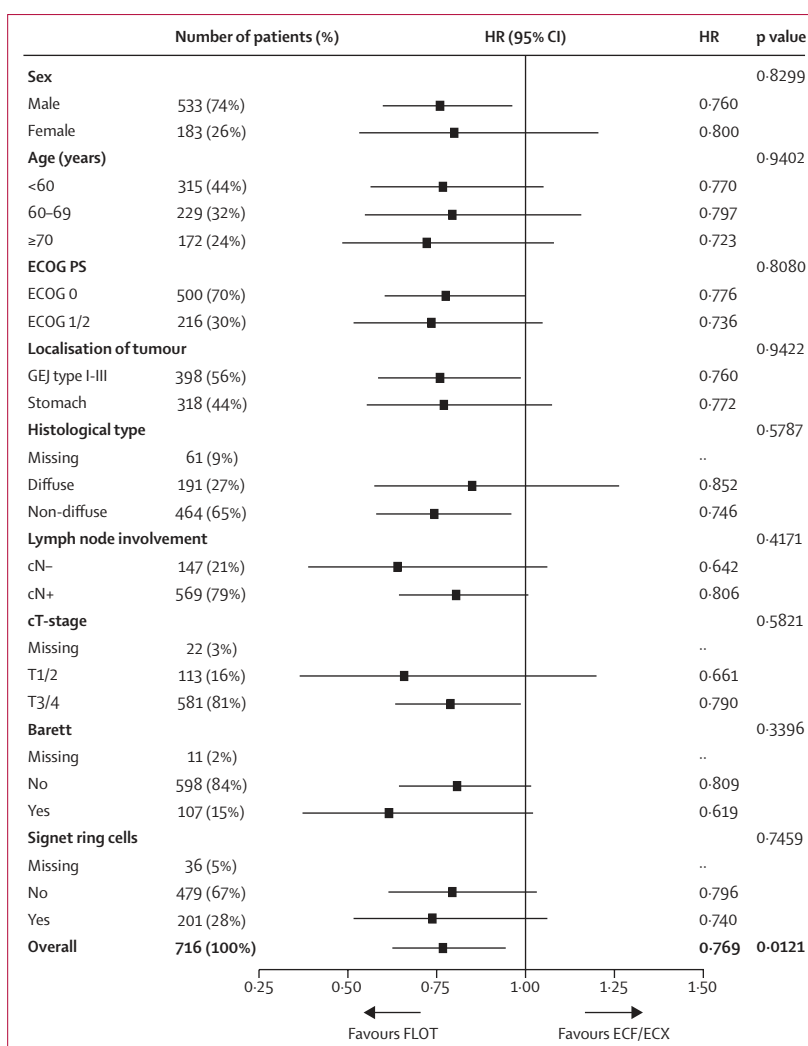
Regarding surgical morbidity and mortality, similar results were observed in both arms in terms of 30-day postoperative death rates (2% in the FLOT group and 3% in the ECF/ECX group) and surgical complications (51% in the FLOT group and 50% in the ECF/ECX group). The numbers are consistent with data recently reported as benchmarking in high-volume centres based on 2704 resections (30-day mortality of 2.4%, 90-day mortality of 5%, and a complication rate of 59%)<sup>22</sup> and, thus, add further weight to the results of previous studies, indicating that preoperative chemotherapy does not increase perioperative morbidity and mortality.<sup>2,4</sup> The 90-day mortalities in our trial were 8% in the ECF/ECX group and 5% in the FLOT group. Notably, in our study, in which 80% of patients had a T3/T4 and N+ stage, the 90-day mortality probably reflects the aggressive nature of the disease rather than the surgical mortality.

The chemotherapy toxicity profiles in both arms were expectedly different but roughly consistent with previous studies<sup>2,7,13,14</sup> for each of the regimens. The most frequent grade 3 or 4 toxicity was neutropenia observed in approximately 40% of patients treated with ECF/ECX versus 50% treated with FLOT. FLOT treatment caused markedly less grade 3 and 4 nausea (7% vs 16%), most likely due to the use of oxaliplatin instead of the highly emetogenic cisplatin. On the other hand, FLOT caused markedly more grade 3 and 4 infections (18% vs 9%) and a clinically relevant incidence of grade 3 or 4 diarrhoea (10% vs 4%). There was no increase in toxic deaths (<1% in each group), hospitalisations for toxicity, discontinuations for toxicity, or serious adverse events with FLOT versus ECF/ECX. Nonetheless, oncologists should be aware of these potential side-effects and special caution should be exercised if they occur in conjunction with neutropenia. For both groups, some toxicities, such

as nausea and vomiting or infections, were reported more frequently in our study compared with previous studies.<sup>2,7,13,14</sup> This could be attributable to a thorough on-site monitoring and source data verification in the present study along with the use of questionnaires to help investigators capturing toxicities during physician-patient consultation. Two aspects might have disadvantaged FLOT in the toxicity analysis. During the treatment, toxicity was evaluated every 2 weeks in the FLOT group and every 3 weeks in the ECF/ECX group. In addition, in the FLOT group, more patients started postoperative therapy and thus were more likely to or had increased opportunity to report toxicity.

FLOT differs from ECF/ECX in several features. The most important difference appears to be the use of the docetaxel instead of the epirubicin as a third drug, but also, that FLOT is a 2-week regimen, whereas ECF/ECX is a 3-week regimen, and that FLOT contains oxaliplatin instead of cisplatin. Additionally, the schedule and doses of the fluoropyrimidines differ. Therefore, it is difficult to speculate whether other docetaxel-based three-drug regimens such as the parent DCF would be associated with comparable safety and efficacy profiles in the perioperative setting.

Some points and limitations in our study deserve discussion. The 5-year survival rates are an estimation and could change with longer follow-up time as most patients were censored at earlier time points. However, this is similar to most randomised trials evaluating curable patients, and the median survivals, and the 2-year and 3-year survival rates of our trial can be considered robust. Moreover, the sample size calculation was based on median survivals and a prespecified follow-up time (4 years enrolment time and 6 years total follow-up time), which was fully achieved. There was a change in the primary endpoint from disease-free survival to overall survival during the study. This change was performed at the request of the independent scientific committee of the German Cancer Aid based on questions about the validity of disease-free survival as a surrogate for overall survival. As both endpoints were clearly met, we do not see a relevant bias that could affect the interpretation of the results. We used the term disease-free survival to describe the time from randomisation to disease progression, relapse, or death endpoint. The term could be interpreted as imprecise as the patients were with disease during the preoperative period. However, the use of the alternative term progression-free survival would be similarly incorrect because it does not apply for patients undergoing margin-free resection. Regarding the pathological findings, we compared the study groups using the ypT and ypN categories rather than the ypTNM stages to make our results comparable with the results of other important trials of perioperative or preoperative therapy.<sup>2-4</sup> All these trials used the ypT and ypN categories in their reports. As for other perioperative



**Figure 3: Treatment effect on overall survival according to the baseline characteristics of the patients**  
The forest plot shows hazard ratios for death (oblongs) and 95% confidence intervals (I bars). p values stand for test for interaction between treatment and subgroup variable. Non-diffuse type includes the intestinal type, the mixed types, and the types not evaluable according to Lauren. GEJ=gastro-oesophageal junction. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. CI=confidence interval. cN+=nodal positive. cN-=nodal negative.

trials, many patients did not proceed to postoperative therapy. The most frequent reason for this was disease progression or lack of efficacy followed by patients' request and toxicity. This reflects the aggressive biology of the disease and is in line with the findings of the MAGIC trial. The rates of patients proceeding to postoperative therapy could be increased by improved baseline staging methods or, perhaps to a lesser extent, by using more tolerable postoperative regimens.

Marked regional differences exist in terms of the perioperative treatment of patients with localised or locally advanced gastric or gastro-oesophageal junction adenocarcinomas. Perioperative ECF or cisplatin and fluorouracil chemotherapy are used as standards of care in many regions. Both regimens are generally considered equally effective based on the results of previous trials.<sup>2,3,6</sup>

Tumours located in the gastro-oesophageal junction are alternatively treated with preoperative chemoradiation as suggested by the Chemoradiotherapy for Oesophageal Cancer Followed by Surgery Study (CROSS) trial.<sup>4</sup> In our trial, the relative benefit from FLOT was similar among the subgroups of patients with gastric adenocarcinoma or adenocarcinoma of the gastro-oesophageal junction, including the Siewert type I tumours as well as patients with or without Barrett mucosa. Therefore, we propose that, given the results of the present study, FLOT should be regarded as the recommended perioperative chemotherapy for patients with gastric cancer or adenocarcinoma of the gastro-oesophageal junction including Siewert type I tumors, and consequently the new standard of care for patients who would have been candidates for perioperative ECF or CF. Whether adenocarcinomas of the gastro-oesophageal junction should be treated with perioperative FLOT or with preoperative chemoradiation, remains an open question. Head-to-head comparisons are absent and it is difficult to draw conclusions from cross-trial comparisons because these are limited by differences in the design of the studies, patients' characteristics, and regional differences in surgical management. Whether adenocarcinomas of the gastro-oesophageal junction should be treated with perioperative FLOT or with preoperative chemoradiation, is currently being evaluated in two phase 3 trials: the Perioperative Chemotherapy (FLOT Protocol) Compared To Neoadjuvant Chemoradiation (CROSS Protocol) in Patients With Adenocarcinoma of the Esophagus Trial (ESOPEC) compares the FLOT4 concept with the CROSS concept in patients with oesophageal and gastro-oesophageal junction adenocarcinoma (NCT02509286), and the Trial of Preoperative Therapy for Gastric and Esophagogastric Junction Adenocarcinoma (TOPGEAR) evaluates the combination of preoperative chemoradiation and perioperative chemotherapy (NCT01924819). The results of these and other ongoing trials could help us to understand which patients are more likely to benefit from which treatment method. Integrating individualised, biomarker-driven therapy and immunotherapy into the perioperative concepts, such as human epidermal growth factor receptor 2 (HER2) antibodies for patients whose tumors overexpress the HER2 protein or check-point antibodies, might also help to further improve the outcome the patients.

In conclusion, perioperative chemotherapy with FLOT improved overall survival in patients with adenocarcinoma of the gastric adenocarcinoma or gastro-oesophageal junction adenocarcinoma as compared with perioperative chemotherapy with ECF or ECX.

#### Contributors

S-EA-B had the original idea, designed the study, was responsible for protocol development, wrote the report, and did the literature search. MG developed the figures. CP was responsible for project management. All authors except CP, MG, and FSO recruited patients into the study and collected data. All authors contributed to data interpretation and contributed to revising the manuscript.

#### Declaration of interests

S-EA-B has an advisory role with Merck, Roche, Celgene, Lilly, Nordic Pharma, Bristol-Myers Squibb and MSD Sharp & Dohme; is a speaker for Roche, Celgene, Lilly, Nordic Pharma, AIO gGmbH, MCI, promedicis, and Forum für Medizinische Fortbildung; he is CEO/founder of IKF Klinische Krebsforschung GmbH; and has received research grants from Sanofi, Merck, Roche, Celgene, Vifor, Medac, Hospira, Lilly, Bristol-Myers Squibb, German Cancer Aid (Krebshilfe), German Research Foundation, and the Federal Ministry of Education and Research. MS is a consultant to AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, and Roche; has received honoraries for CME presentations with Abbvie, Alexion, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Lilly, MSD, Novartis, and Pierre Fabre; his institution has received research funding from Boehringer Ingelheim, Bristol-Myers Squibb, and Novartis; and he holds patents with Universität Duisburg-Essen. None of the above is related to or has influenced the work presented here. HS has an advisory role for BMS, Lilly, and Novartis and has received research grants from Sanofi. CT is a speaker for Roche. TOG has an advisory role with Lilly, MSD Sharp & Dohme, Shire, Bayer, Celgene, and Servier; is a speaker for Lilly, MCI, MSD Sharp & Dohme; and has received research grants from German Research Foundation. KS has an advisory role with Amgen, Bristol-Myers Squibb, Merck, Novartis, and Roche; is a speaker for Roche; and has received travel support and congress fee compensation from Abbvie, Bristol-Myers Squibb, Celgene, and Lilly. GMH reports fees for advisory role from BMS, Taiho, Nordic, Lilly, and MSD; honoraria from Roche and Pfizer, travel grants from Amgen, Ipsen, Celgene, and BMS; research funding is provided by Nordic and Taiho Pharmaceuticals. JM is a consultant to Roche, Bristol-Myers Squibb, and Sanofi-Aventis Lilly and reports personal fees from Amgen. SK is a consultant to AstraZeneca, Amgen, Bristol-Myers Squibb, Lilly, Merck, MSD Sharp & Dohme, Sanofi-Aventis, Servier, Shire, and Roche; received Honoraries for CME presentations from AstraZeneca, Amgen, Bristol-Myers Squibb, Lilly, Merck, MSD Sharp & Dohme, Roche, Sanofi-Aventis, Servier, and Shire. His institution received research funding from Bristol Myers-Squibb, Celgene, Lilly, Merck, Roche and Servier. SD had an advisory role with Amgen and has an advisory role with Bristol-Myers Squibb and is a speaker for Sanofi, Recordati, Amgen and Falk. MP reports personal fees from Roche Pharma AG, Amgen AG, MSD Sharp & Dohme GMBH, MCI Deutschland GmbH, Merck Serono, Sanofi Aventis, BMS, Baxalta-Shire, Chugai, Celgene, Roche Pharma AG, Servier, Dres-Schlegel + Schmidt, and Lilly; and is a consultant in haematology and oncology and an employee of Universitätsklinikum Knappschafts-Krankenhaus Bochum, Ruhr university bochum. WS reports grants from German Cancer Aid, during the conduct of the study; personal fees from AiCuris, Amgen, Apcteth, Indivumed, Merck Serono, 4SC, Deutschlandfunk (DLF Deutsches Ärzteblatt, Elsevier Verlag, Springer Verlag, Westdeutscher Rundfunk (WDR), personal fees from Zweites Deutsches Fernsehen (ZDF), Falk Foundation, Lilly Deutschland GmbH, MCI, Pfizer, Roche, Sanofi, Aventis, Siemens Healthcare, Dres-Schlegel + Schmidt, Deutscher Ärzteverlag, Labor Berlin-Charité Vivantes Services GmbH, and Servier Deutschland; grants from Sysmex Deutschland GmbH - Research Corporation, investigator staff honoraria from Ganymed, other from Celgene, other from Hoffmann La Roche, outside the submitted work. DP has an advisory role with Roche, Lilly, PharmaMar, and Clinigen; is a speaker for Lilly and PharmaMar and has received research grants from Lilly, PharmaMar, Novartis, and Clinigen. PT-P has an advisory role with Roche, MSD Sharp & Dohme, Bristol-Myers Squibb, Merck, and Nordic, and had travel expenses covered by Roche, Merck, and Lilly, outside the submitted work. JT reports personal fees from Amgen, Bayer Healthcare, Bioprojet, Bristol-Myers Squibb, Celgene, Daichi Sankyo, Ipsen, Imclone, Roche, Servier, and Shire, outside the submitted work. MM has compensated consultant or advisory relationships with Falk foundation, Nordic, Amgen, AstraZeneca, MCI, Lilly, MSD, MerckSerono, Pfizer, BMS, Onyx, and Roche and received research grants by Amgen, BMS, MSD, MerckSerono, Taiho, Roche, AIO gGmbH, and EORTC. UMM has an advisory role with Merck, Roche, Celgene, Lilly, Bristol-Myers Squibb, Sanofi, and MSD Sharp & Dohme. NH has an advisory role with Sanofi, Roche, Amgen, Lilly, Servier, and Bristol-Myers Squibb and is a speaker for Sanofi, Roche, Amgen, Merck, Celgene, MSD Sharp & Dohme, and Servier. VH reports honoraria from Merck, Roche, Celgene, AMGEN, Sanofi, Lilly, SIRTEX,

Boehringer Ingelheim, Taiho, and Servier; consulting or advisory board activities for Merck, Roche, AMGEN, Sanofi, SIRTEX, Servier, Celgene, Boehringer Ingelheim, Halozyme, MSD, and BMS; research funding from MERCK, Roche, AMGEN, SIRTEX, Servier, Celgene, Boehringer-Ingelheim, and Shire and travel accommodation expenses from MERCK, Roche, AMGEN, SIRTEX, Servier, Shire, MSD, and BMS. WOB has served on an advisory board for Astellas and has received honoraria and travel reimbursement from Astellas, Baxter, Integra, MCI Deutschland, Medupdate GmbH, MerckSerono, and TEVA. DMB has an advisory role with Boehringer Ingelheim, Bristol-Myers Squibb, and Roche. GF has received a research grant from Merck-Serono and has received honoraries from Merck-Serono, Roche/Genentech, Sanofi-Aventis, Bristol-Myers Squibb, Merck Sharp Dome, Servier, Lilly, Amgen, Mundipharma, and Shire. RDH has an advisory role with Merck, Roche, Boehringer Ingelheim, Sanofi-Aventis, Lilly, Bristol-Myers Squibb, and MSD Sharp & Dohme; is a speaker for Roche, Merck, Lilly, Sanofi-Aventis, Bristol-Myers Squibb, and MSD Sharp & Dohme and has received research grants from Amgen, Sanofi, Merck, Roche, medac, and German Cancer Aid (Krebshilfe). H-GK reports personal fees from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, MSD, Pierre Fabre, Roche, personal fees from PharmaMar, and Pfizer, outside the submitted work. WF reports personal fees from Abbot, AbbieVie Deutschland, Bio Merieux, Boehringer Ingelheim, Falk, Kibion, Norgine, Pfizer, and Reckitt Benckiser, outside the submitted work. RM reports non-financial support from Amgen, Merck, and Novartis, outside the submitted work. GS has an advisory role with Novartis and Sanofi-Aventis. All other authors declare no competing interests.

#### Data sharing

Data collected for the study, including individual participant data and a data dictionary will not be made available to others.

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