Trastuzumab in combination with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel as perioperative treatment for patients with human epidermal growth factor receptor 2-positive locally advanced esophagogastric adenocarcinoma: A phase II trial of the Arbeitsgemeinschaft Internistische Onkologie Gastric Cancer Study Group

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Abstract
Perioperative chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin and docetaxel (FLOT) is a mainstay in the treatment of esophagogastric adenocarcinomas (EGA). Trastuzumab improved survival when added to chemotherapy in patients with HER-2-positive metastatic EGA. We investigated the combination of trastuzumab and...
FLOT as perioperative treatment in patients with locally advanced EGA. A multicenter phase II study evaluated the efficacy and toxicity of perioperative FLOT (24-hours 5-FU 2600 mg/m², leucovorin 200 mg/m², oxaliplatin 85 mg/m², docetaxel 50 mg/m², trastuzumab 6 mg/kg then 4 mg/kg d1, repeated d15 for four cycles preoperatively and postoperatively followed by 9 cycles of trastuzumab monotherapy) in patients with HER-2 positive EGA. Patients had ≥cT2, any N, M0 EGA. The primary endpoint was the rate of centrally assessed pathological complete response (pCR). Secondary endpoints comprised disease-free (DFS) and overall survival (OS), R0 resection rate, toxicity and surgical morbidity. Fifty-six evaluable patients (median age 62 years) were included; n = 40 had tumors originating from the esophagogastric junction; T stage was (cT2/3/4/unknown): 4/42/8/2; n = 50 patients had cN+ disease. Main adverse events grades 3-4: leukopenia (17.9%), neutropenia (46.6%) and diarrhea (17.0%). All patients underwent tumor resections. R0 resection rate was 92.9%. Eight patients had anastomotic leakage. One postoperative death occurred. pCR was found in 12 patients (21.4%) and a further n = 14 patients (25.0%) had near complete response. Median DFS was 42.5 months and the 3-year OS rate was 82.1%. The primary endpoint of achieving a pCR >20% was reached. No unexpected safety issues were observed. Survival data are promising.

**KEYWORDS**
docetaxel, esophagogastric adenocarcinoma, perioperative treatment, trastuzumab

**What’s New?**
Perioperative infusion of 5-fluorouracil, leucovorin, docetaxel, and oxaliplatin (FLOT) benefits survival in patients with resectable esophagogastric adenocarcinoma (EGA). Up to one-fifth of EGAs, however, exhibit overexpression or amplification of human epidermal growth factor receptor (HER2), the standard-of-care for which is platinum-based chemotherapy plus trastuzumab. Here, in a phase II trial, safety and efficacy of perioperative FLOT plus trastuzumab were investigated for HER2-positive EGA. Combined trastuzumab and FLOT generally was safe, with expected mild adverse events. The primary endpoint, pathological complete remission, was reached, with about half of patients achieving complete or near-complete remission. Survival data were promising, warranting randomized trials.

1 | **INTRODUCTION**

The prognosis of patients with locally advanced resectable esophagogastric adenocarcinoma (EGA; comprising gastric cancer and adenocarcinoma of the gastroesophageal junction) has been significantly improved during the past years by using multimodality treatment. Compared to surgery alone, preoperative radiochemotherapy consisting of weekly carboplatin and paclitaxel as well as 41.4 Gy applied to the primary tumor region (CROSS regimen) prolonged overall survival of patients with esophageal cancer (adenocarcinoma, n = 275; squamous cell carcinoma, n = 84). More recently, perioperative chemotherapy using biweekly infusional 5-fluorouracil, leucovorin, docetaxel and oxaliplatin (FLOT) led to a significant disease-free and overall survival benefit for patients with EGA (n = 716) compared to the former reference regimen, epirubicin, cisplatin and 5-FU or capecitabine (ECF or ECX). Thus, FLOT is regarded as a new standard for the perioperative treatment of patients with EGA.

Overexpression and amplification of the human epidermal growth factor receptor (HER2) is found in about 15%-20% of all cases with EGA, predominantly in tumors deriving from the gastro-esophageal junction with an intestinal tumor type according to Lauren. Inconsistent data in terms of a potential prognostic impact of HER2 positivity has been reported, while HER2 positivity is unequivocally regarded as a predictive marker for the treatment with trastuzumab. When added to platinum-based chemotherapy, trastuzumab led to a survival benefit for patients with metastatic or advanced, unresectable HER2 positive EGA (ie, immunohistochemistry 3+ and/or fluorescence in situ hybridization positivity [HER2:chromosome 17 ratio ≥2.0]) in the ToGA trial. The current phase II trial sought to assess efficacy and safety of the combination of trastuzumab and FLOT in patients with locally advanced, resectable esophagogastric adenocarcinoma.
PATIENTS AND METHODS

2.1 Study design and patient eligibility criteria

Eligible patients had histologically confirmed HER2-positive adenocarcinoma of the stomach or gastroesophageal junction of a clinical stage ≥cT2 and/or ≥cN+ and no clinical evidence of distant metastases. HER2-positivity was determined by an accredited local pathology (no central review was in place) and was defined as follows: HER2 3+ (IHC) or HER2 2+ (IHC) with amplification proven by FISH, SISH or CISH. Main eligibility criteria comprised: Patients aged ≥18 years; ECOG ≤2; adequate hematological, hepatic and renal function parameters (leukocytes ≥3000/mm³, platelets ≥100 000/mm³; serum creatinine ≤1.5 × upper limit of normal [ULN], or GFR > 40 mL/min; bilirubin ≤1.5 × ULN, AST and ALT ≤3.5 × ULN, alkaline phosphatase ≤6 × ULN); normal cardiac ejection fraction, as assessed by echocardiography. No preceding cytotoxic or targeted therapy. Main exclusion criteria were: clinically significant active coronary heart disease, cardiomyopathy or congestive heart failure (NYHA III-IV); clinically significant valvular defect; history of other malignancies not curatively treated and without evidence of disease for more than 5 years, except for curatively treated basal cell carcinoma of the skin and in situ carcinoma of the cervix; known brain metastases; peripheral polyneuropathy > NCI Grade II.

The clinical stage was determined by esophagogastroduodenoscopy, endoscopic ultrasound, and computed tomography or magnetic resonance imaging. Diagnostic laparoscopy was recommended for all patients with suspected peritoneal involvement. All patients gave written informed consent.
2.2 Treatment plan and trial procedures

FLOT was administered for four preoperative cycles followed by four postoperative cycles. Each 2-week cycle of FLOT consisted of docetaxel 50 mg/m², oxaliplatin 85 mg/m², leucovorin 200 mg/m² and 5-FU 2600 mg/m² as 24-hour infusion on day 1, respectively. Trastuzumab was administered at a dose of 4 mg/kg body weight in combination with FLOT (6 mg loading dose at first administration), iv over 1 hour on day 1 of each cycle, as well. After the forth cycle of postoperative HER-FLOT, trastuzumab was administered three-weekly as monotherapy at a dose of 6 mg/kg body weight, iv over 1 hour for another nine cycles. Patients, who were not eligible for postoperative chemotherapy, were allowed to receive trastuzumab monotherapy.

Surgery was scheduled 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 I gastroesophageal junction cancers and gastrectomy with transhiatal distal esophagectomy plus D2 lymphadenectomy for types II and III gastroesophageal junction cancers. For gastric cancer, total or subtotal distal gastrectomy with D2 lymphadenectomy was performed.

Patients were assessed with regard to medical history, physical examination, body weight, ECOG performance status, complete blood count and blood chemical tests at baseline and prior to start of every cycle. Restaging by means of computed tomography or magnetic resonance imaging and endoscopy was performed prior to surgery. Follow-up included computed tomography or magnetic resonance imaging every 3 months until disease progression, relapse or death.

2.3 Study endpoints

Primary objective of the study was to estimate the efficacy of the HER-FLOT regimen regarding the rate of pathological complete responses (pCR) according to the regression grading published by Becker et al (percentage of patients with pCR referring to the total

| TABLE 1 | Patient and disease characteristics |
| --- | --- |
| Characteristics of ITT population | N | % |
| Age, years, median (range) | 62 (32-86) |  |
| Gender, male | 41 | 73.2 |
| ECOG performance status |  |  |
| 0 | 41 | 73.2 |
| 1 | 15 | 26.8 |
| Localization of primary tumor |  |  |
| Esophagogastric junction | 40 | 71.4 |
| Siewert 1 | 17 | 30.4 |
| Siewert 2 and 3 | 23 | 41.0 |
| Stomach | 16 | 28.6 |
| HER2 status |  |  |
| 2+ | 8 | 14.3 |
| 3+ | 48 | 85.7 |
| Clinical tumor stage |  |  |
| T2 | 4 | 7.1 |
| T3 | 42 | 75.0 |
| T4 | 8 | 14.3 |
| Unknown | 2 | 3.6 |
| Clinical nodal stage |  |  |
| cN0 | 6 | 10.7 |
| cN1 | 50 | 89.3 |
| Lauren type |  |  |
| Diffuse | 9 | 16.1 |
| Intestinal | 30 | 53.6 |
| Mixed | 4 | 7.1 |
| Unknown | 13 | 23.3 |
| Grading |  |  |
| G1 | 1 | 1.7 |
| G2 | 25 | 44.6 |
| G3 | 25 | 44.6 |
| Unknown | 5 | 8.9 |
| Left-ventricular ejection fraction | Median (range) | 65.0 (55.0-79.0) |

Abbreviations: ECOG, Eastern Cooperative Oncology Group.

| TABLE 2 | Treatment-emergent adverse events (graded according to NCI CTC criteria v. 4.0) grades 3-4 during the whole treatment period |
| --- | --- |
| Adverse events in the ITT population | N | % |
| Serious adverse events | 30 | 53.6 |
| Adverse events grade ≥ 3 | 52 | 92.2 |
| Hematological |  |  |
| Leukopenia | 10 | 17.9 |
| Neutropenia | 26 | 46.6 |
| Anemia | 3 | 7.1 |
| Thrombocytopenia | 1 | 1.8 |
| Gastrointestinal |  |  |
| Diarrhea | 10 | 17.9 |
| Nausea | 4 | 7.1 |
| Vomiting | 4 | 7.1 |
| Infections and infestations | 12 | 21.4 |
| Fatigue | 4 | 7.1 |
| Hypertension | 3 | 5.4 |
| Thrombosis | 3 | 5.4 |
| Elevated transaminases | 2 | 3.6 |
| Renal failure | 2 | 3.6 |
| Cardiac failure | 1 | 1.8 |

Note: Indicated is the worst grade of toxicity per patient (N = 56). No grade 5 toxicity occurred.
number of enrolled and eligible patients [Full analysis set, FAS]. The Becker grading refers to the regression of the primary tumor only and does not include the assessment of nodal metastases. Evaluation was done centrally by a reference pathologist [A.T.].

Secondary objectives comprised the evaluation of R0 resection rate, disease-free survival (DFS), overall survival (OS), including survival rates after 1, 2 and 3 years, pCR as a surrogate endpoint, perioperative morbidity and mortality, safety and tolerability of the combination regimen.

2.4 | Statistical considerations

Based on the available experience with FLOT, a pCR rate after neoadjuvant chemotherapy alone was assumed to be about 15%. The statistical calculation was based on the following premises and assumptions: the experimental therapy would be rated as insufficiently active, if the observed pCR rate was 10% or lower. On the other hand, the experimental therapy would be considered as promising for further development, if the true pCR rate amounted to 20% or more.

The probability to accept the experimental therapy as promising (>20% pCR), in spite of a true pCR rate of ≤10% was set at 10% (type I error). The probability to reject the experimental therapy as not sufficiently efficient (≤10%), although the true pCR rate was promising (>20%) was set at 20% (type II error, corresponding to a power of 80%). According to these parameters, and using a standard single-stage Fleming phase II design, \( n = 53 \) patients evaluable for efficacy had to be recruited. OS was defined as time from randomization to death, DFS as time to disease progression, relapse, or death whichever occurred first. DFS and OS were analyzed using the Kaplan-Meier method. Time-to-event comparisons between patients with or without pCR were tested with the log-rank model. All other groups were compared using the chi-square test. \( P \)-values were 2-sided. Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The analysis was conducted using SAS software program version 9.3.

3 | RESULTS

3.1 | Patient populations and characteristics

Fifty-eight patients were enrolled between January, 2012 and July, 2013 (CONSORT; Figure 1). Two patients were excluded due to major
protocol violations (presence of peritoneal carcinomatosis, \(n = 1\); HER2 negative tumor \(n = 1\)). Thus, 56 patients comprise the full analysis set (FAS), which is the basis for all safety and efficacy analysis reported herein.

Patients had a median age of 62 years (range, 32-86). Fourteen patients (25.0%) were ≥70 years. All patients had an ECOG of zero or 1. Forty-one (73.2%) of the patients were males. Almost three quarters of the tumors originated from the esophagogastric junction and
3.2 | Treatment administration

The majority of tumors had a cT3 status with positive lymph nodes (Table 1).

3.2 | Treatment administration

The overall study treatment duration ranged to a maximum of 434 days, with a mean of 285 ± 133 days and a median of 349 days. All patients received the planned four preoperative cycles. Forty-five patients (80.4%) started postoperative treatment, and n = 28 (50.0%) completed all planned chemotherapy cycles. The entire study treatment (8 cycles of chemotherapy plus 9 cycles of additive trastuzumab monotherapy) was administered to 25 patients (44.6%). The overall number of treatment cycles is shown in Figure 1.

The mean relative dose intensity, based on cycles actually administered, amounted to 94% for 5-FU, 97% for leucovorin, 94% for oxaliplatin, 91% for docetaxel and 99% for trastuzumab. The corresponding numbers and proportions of patients with major dose reduction, defined as receiving less than 90% of the planned dose of these drugs, were 14 (25%), 9 (16%), 16 (29%), 17 (30%) and 2 (4%), respectively. Cycle delays—defined as more than 2 days delay of a combination therapy cycle, and more than 3 days in case of trastuzumab monotherapy—occurred more frequently during the combination treatment phase than in the single agent period. Preoperative cycles number 2, 3 and 4 were delayed in a total of 15, 8 and 10 patients (26.8%, 14.3% and 17.9%, respectively).

3.3 | Adverse events

The frequency of events with severity grade ≥ 3 during the whole treatment period (maximum by category and patient) is summarized in Table 2. The most frequently observed adverse events grades 3 and 4 were leukopenia, neutropenia, diarrhea and infections. In terms of trastuzumab associated treatment emergent adverse events three patients exhibited peripheral edema (grades 1/2), and four had infusion related reactions (all grade 1 and 2). One case of severe cardiac disorder caused by trastuzumab was reported.

3.4 | Surgery and surgical morbidity

Surgical results are depicted in Table 3. All patients underwent surgery and had resection of the primary tumor. In 92.9% of the patients, R0 resection was possible. Twenty-five (44.6%) of the patients had trans-esophageal esophagectomy. About half of the patients had postoperative complications, of whom eight required reoperation. One postoperative death occurred.

3.5 | Pathological downstaging (primary endpoint)

The rate of centrally confirmed pathological complete responses was 21.4% (12 out of 56 patients; 95% confidence interval 11.6%-34.4%) (Table 4). Thus, the primary endpoint was reached. No impact of tumor location (ie, esophagogastric junction vs gastric cancer) on the likelihood of achieving a pCR was seen (pCRjunction 22.5% vs pCRgastric 18.8%, P > .99). Interestingly, no patient with a primary tumor with diffuse type histology achieved a pCR (0 out of nine patients), while those with intestinal histology exhibited a 33.3% pCR rate (10 out of 30 patients with information on Laurén grading; P = .07).

Another 14 patients (25.0%) had subtotal response (<10% vital tumor cells). In terms of assessment by local pathologists, 12 patients exhibited ypT0 ypN0 and 1 patient had ypT0, ypN1. A median of 27 lymph nodes were pathologically assessed. Lymph node negativity was reported in 33 patients.

3.6 | Disease-free and overall survival

Disease-free and overall survival are depicted in Figures 2 and 3. After a median follow-up of 36 months, n = 19 patients had a DFS event. Median DFS was 42.5 months (95% CI 36.5—not reached). A total of n = 13 patients had died. Median survival had not yet been reached at the end of observation (95% CI 42.5—not reached). One-year, two-years and 3-year survival rates were 96.4% (95% CI 87.7-99.6), 89.3% (78.1-96.0) and 82.1% (69.6-91.1), respectively. Both, disease-free and overall survival were numerically improved for patients showing a centrally confirmed pCR: HRDFS 0.19, 95% CI 0.03-1.43, P = .07; HROS 0.34, 95% CI 0.04-2.62, P = .27. Neither tumor location (esophagogastric junction vs gastric cancer) nor Laurén classification

| TABLE 5 | Cross-trial comparison of key results between FLOT4 and HER-FLOT |
|---------|-------------------|
| FLOT4   | HER FLOT          |
| Age, years (median) | 62 | 62 |
| Gender, male (%)   | 75 | 73 |
| Localization esophagogastric junction (%) | 55 | 71 |
| cT3/4 tumor (%)    | 83 | 89 |
| Received all four cycles preoperative (%) | 90 | 100 |
| R0 resection (%)   | 84 | 93 |
| Rate of pathological complete response (%) | 16 | 21 |
| Toxicity NCI CTC grade 3-5 (%) |
| Diarrhea | 10 | 17 |
| Vomiting | 7 | 7 |
| Nausea | 2 | 7 |
| Leukopenia | 27 | 18 |
| Neutropenia | 51 | 46 |
| Median follow-up (months) | 43 | 36 |
| Disease-free survival, median (months); 95% CI |
| 30; 31-41 | 42; 36.5-n/r. |
| 3-year survival (%) | 57 | 82 |

Note: Patients in FLOT4 are not selected for HER2 status.
Abbreviation: n.r., not reached.
(diffuse vs intestinal histology) had an impact on DFS or overall survival.

4 | DISCUSSION

FLOT is a standard of care for perioperative treatment for patients with locally advanced EGA. In the randomized phase III FLOT4 trial including more than 700 patients, FLOT increased the rates of curative surgery and prolonged disease-free and overall survival as compared to ECF or ECX.² The relative effect from FLOT was consistent across all subgroups and sensitivity analyses. There was no increase in surgical morbidity and mortality, reoperation, or hospitalization times.

In an attempt to improve these results within the subgroup of patients with HER2 positive EGA, the HER-FLOT study was initiated. Patients with HER2 positive EGA were treated with the standard FLOT regimen (ie, 4 cycles preoperative and 4 cycles postoperative) in combination with trastuzumab, a monoclonal antibody against HER2 which is approved for the treatment of patients with metastatic EGA in combination with 5-FU and cisplatin. Trastuzumab treatment was foreseen for a total of 12 months in analogy to the adjuvant treatment of women with resected breast cancer.

HER-FLOT met the primary endpoint of achieving a pCR rate above 20%. Twelve out of fifty-six patients (21.4%) had no viable tumor cells within the primary tumor area as assessed by central pathology. This pCR rate is among the highest reported in a clinical prospective trial using central pathology. Moreover, 46.4% of the patients achieved either a total (pCR) or a subtotal response to treatment thus resulting in excellent tumor remissions in about half of the patients.

The FLOT4 trial had included 356 patients in the FLOT arm in an identical treatment setting using the same inclusion criteria and the same institution for central pathological review. Thus, results of FLOT4 provide an opportunity to put the data of the HER-FLOT trial in context although FLOT4 has not reported results according to HER2 status. Table 5 summarizes data from these studies. This cross trial comparison gives the impression of comparable patient and tumor characteristics and similar adverse event profiles. The centrally assessed pCR rate was 21.4% (95% CI 12-34) in HER-FLOT and 16% (95% CI 10-23) in FLOT4 in 128 patients from the randomized phase II part.⁷ The pCR rate is therefore numerically higher, but the confidence intervals overlap. Finally, this comparison suggests the hypothesis that survival may be improved by using trastuzumab (3-year survival 82% vs 57%). In terms of surgical morbidity, the rate of anastomotic leakage in the HER-FLOT trial was numerically higher (14.3%) than in the FLOT4 trial (8.7% for FLOT and 11.4% for ECF/ECX, data on file). The somewhat higher rate of anastomotic leakage observed within the current trial may be explained by a higher amount of patients with EGA tumors included in the current trial and the fact that all patients were resected in HER-FLOT while more patients in FLOT4 did not undergo surgery. On the other hand, we found identical rates of anastomotic leakage within the PETRARCA trial (FLOT ± trastuzumab/pertuzumab) (10% in both arms; data on file).⁸

Two arguments could be put forward against the claim that the survival results achieved with HER-FLOT are promising. Firstly, it may be argued that HER2 is a good prognostic marker regardless of treatment. In contrast to this assumption, several case series suggest that HER2 overexpression or amplification is associated with worse prognosis,⁹-¹¹ whereas other studies have shown HER2 expression to have no prognostic significance at all.¹² However, an investigation including esophageal adenocarcinoma came to a different conclusion.¹³ A recent study in Western patients with metastatic EGA concluded that HER2 status alone was not an independent prognostic marker.¹⁴ In all, a clear argument that the promising survival in HER-FLOT may be explained by a prognostic effect cannot be made.

Secondly, HER2 positivity may make locally advanced EGA more susceptible and responsive to perioperative chemotherapy. This hypothesis was investigated retrospectively using data from the MAGIC trial which investigated the addition of ECF to surgery.¹⁵ Diagnostic biopsies and/or resection specimens were collected from 415 out of 503 trial patients and HER2 was evaluated by immunohistochemistry (IHC) and in situ hybridization. The prognostic and predictive impact of HER2 status was assessed. The authors found that HER2 status was neither prognostic, nor predicted enhanced benefit from chemotherapy (benefit of HER2 positive tumors from ECF vs surgery alone 0.74; HER2 negative HR 0.58; interaction test negative). The authors concluded that HER2 status was not an independent marker for benefit from perioperative chemotherapy in EGA.

Most of the HER-2 positive esophagealgastric adenocarcinomas originate from the esophagogastric junction, and these tumors are treated with preoperative chemoradiotherapy as an alternative to perioperative chemotherapy in some centers. Trastuzumab and pertuzumab have been investigated in combination with chemoradiotherapy (based on the CROSS regimen). In this feasibility phase II trial, Strees et al reported good tolerability and pathologic complete responses in 13 out of 40 patients.¹⁶ With a median follow-up of 32 months, 3-year OS was 72%, and compared adequately with the results of the HER-FLOT study (3-year OS, 82%).

Meanwhile, the results of two randomized trials have been reported as oral presentations at the ASCO meeting 2020 for both scenarios, that is, addition of HER2 directed drugs to chemotherapy as well as chemoradiotherapy. The AIO PETRARCA trial (FLOT ± trastuzumab/pertuzumab; NCT02581462) albeit stopped prematurely (after the negative results from the JACOB study had been reported)¹⁷ during the randomized phase II part of the study after inclusion of 80 patients reported a significantly higher pCR rate in the investigational arm (35 vs 12%; \(P = .019\)) and a preliminary DFS benefit.¹⁸ Contrarily, the addition of trastuzumab to the CROSS regimen within the RTOG 1010 randomized phase III trial (NCT01196390) did not result in any benefit, neither in terms of pCR nor DFS.¹⁹ Thus, the results of the EORTC INNOVATION trial (platinum-based chemotherapy ± trastuzumab or trastuzumab/pertuzumab; NCT02205047),²⁰ are eagerly awaited and will help to elucidate a potential role of anti-HER-2 compounds in the perioperative treatment of patients with locally advanced, resectable esophagealgastric adenocarcinoma. Until the results from the INNOVATION trial have been reported and
mature survival results from PETRARCA are available we would refrain from using HER2 targeted agents outside of clinical trials in the perioperative setting, neither trastuzumab nor the combination of both, trastuzumab and pertuzumab.

In all, the pathological response rate in HER-FLOT and good safety data both, in terms of treatment emerging adverse events and—with the exception of anastomotic leakage—surgical morbidity as well as promising survival results justify further trials with HER2 targeted agents in the perioperative treatment of HER-positive esophagogastric adenocarcinoma. Albeit negative phase III trials have been reported for T-DM1 and pertuzumab in the metastatic setting,17,21 those drugs and newer HER2 targeting agents22 may be beneficial when used in the perioperative setting.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT
The HER-FLOT “Arbeitsgemeinschaft für Internistische Onkologie” (AIO) phase II trial was an investigator-initiated clinical trial (Clinicaltrials.gov: NCT01472029). The study was approved by the institutional review board of all participating centers and conducted according to Good Clinical Practice guidelines, the Declaration of Helsinki and local laws. All participating patients provided written informed consent.

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