Received: 26 May 2021 | Revised: 24 September 2021 | Accepted: 8 October 2021

DOI: 10.1002/ijc.33864

CANCER THERAPY AND PREVENTION

IJC INTERNATIONAL JOURNAL of CANCER

Pazopanib with 5-FU and oxaliplatin as first line therapy in advanced gastric cancer: A randomized phase-II study—The PaFLO trial. A study of the Arbeitsgemeinschaft Internistische Onkologie AIO-STO-0510

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Abstract

VEGF inhibition in gastric cancer has a proven benefit in the second line setting. Pazopanib, an oral tyrosine kinase inhibitor, selectively inhibits VEGFR-1, -2 and -3, c-kit and PDGF-R resulting in inhibition of angiogenesis. This open-label randomized phase II trial (2:1) investigated the efficacy of combining pazopanib with FLO

Abbreviations: AIO, Arbeitsgemeinschaft Internistische Onkologie; BSC, best supportive care; CAPOX, capecitabine/oxaliplatin; ECOG, Eastern Co-operative Oncology Group; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; FLO, 5-fluorouracil, folinic acid, oxaliplatin; FOLFOX, folinic acid, 5-fluorouracil, oxaliplatin; GEJ, gastroesophageal junction; Her2/neu, human epidermal growth factor receptor 2/neu; ORR, overall response rate; OS, overall survival; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin; PDGF, platelet derived growth factor; PFS, progression-free survival; PFSR, progression-free survival rate; SCC, squamous cell cancer; TKI, tyrosine kinase inhibitors; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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Funding information
GlaxoSmithKline Foundation; Novartis

(5-fluorouracil, oxaliplatin) vs FLO alone (internal control arm) as first-line treatment in patients with advanced adenocarcinoma of the stomach and gastroesophageal junction (GEJ). Eighty-seven patients were randomized and 78 patients were eligible and evaluable (PaFLO arm 51 patients, FLO arm 27 patients). The PFS rate at 6 months (primary endpoint) was 34% in the PaFLO arm vs 30% in the FLO arm. Comparing PaFLO with FLO median PFS was 4.66 months (95% confidence interval [CI] 2.87-6.46) vs 4.47 months (95% CI 1.79-7.14) (95% CI, hazard ratio [HR] 0.96 (0.60-1.55), $P = .882$ [exploratory]); median OS was 10.19 months (95% CI 5.46-14.92) vs 7.33 months (95% CI 4.93-9.73), (95% CI HR 1.01 [0.62-1.65], $P = .953$, exploratory), disease control rate was 72% vs 59%. PaFLO was well tolerable, toxicities were slightly higher in the PaFLO arm. Major adverse events were loss of appetite, nausea, fatigue, diarrhea, neutropenia and thrombocytopenia. Adding pazopanib to chemotherapy shows signs of efficacy but no major improvement in this randomized phase 2 trial. The PFS at 6 months in both arms was lower than expected from the literature. Biomarkers identifying subgroups who benefit and novel combinations are needed. ClinicalTrials.gov: NCT01503372.

KEYWORDS
FLO, gastric cancer, GEJ cancer, PaFLO, pazopanib

What's New?

Pazopanib is an oral angiogenesis inhibitor. In this randomized, phase II clinical trial, the authors added pazopanib to standard chemotherapy as a first-line treatment in patients with advanced gastro-esophageal cancer. This combination was compared to chemotherapy alone. The results indicated that the addition of pazopanib to 5-FU/oxaliplatin was well tolerated and showed some efficacy, but didn't yield a major benefit over standard therapy. Further research into other novel treatment combinations, as well as into biomarkers to identify subgroups who might benefit, are urgently needed.

1 | INTRODUCTION

Gastric cancer ranges at sixth place of newly diagnosed cancer cases worldwide, after cancers of the lung, breast, prostate, colon and rectum, and skin (nonmelanoma) with an incidence rate of approximately 1 089 103 cases. Gastric cancer is the third most common cause of death from cancer, accounting for approximately 769 000 deaths per year globally.[1] At the time of diagnosis, 30% to 40% of patients with adenocarcinoma of the stomach and gastroesophageal junction cancers (GEJ) are candidates for potentially curative surgery, but 50% to 60% show recurrence of their disease.

Overall survival (OS) can be significantly improved with systemic first line chemotherapy in comparison to best supportive care (BSC) and combination chemotherapy further improves survival rates. The standard regimen is a platin-/fluoropyrimidine-based chemotherapy, where applicable, supplemented by anthrazyclines, taxanes and trastuzumab in case of HER2-neu positivity.[2-4] The Real-2 phase III trial evaluated the effect of oral capecitabine and oxaliplatin as alternatives to infused fluorouracil and cisplatin for untreated advanced gastric and GEJ cancer. In a noninferiority design, the trial revealed that oxaliplatin can replace cisplatin and capecitabine infusional 5-FU.[5] The effect of either oxaliplatin or cisplatin in combination with fluorouracil and folinic acid was further investigated in the phase III trial of the AIO (Arbeitsgemeinschaft Internistische Onkologie) and showed improved tolerability and same efficacy of the combination of 5-FU and oxaliplatin compared to 5-FU and cisplatin.[6] Based on these data the combination of oxaliplatin and 5-FU has been widely adopted as a standard and is recommended in international treatment recommendations, for example, by expert opinions of the EORTC (European Organisation for Research and Treatment of Cancer).

Inhibition of neoangiogenesis is an approach with proven efficacy in the treatment of advanced gastric cancer. VEGF (vascular endothelial growth factor) and PDGF (platelet derived growth factor) act as stimulating factors of angiogenesis by binding to specific receptors, whose activation stimulates a signaling cascade resulting in endothelial cell migration, induction of proteinases, extracellular matrix remodeling and increased vascular permeability involved in forming new blood vessels.[7] Angiogenesis plays a central role in genesis and metastatic spread of tumor cells in various tumor types as liver, lung, breast, kidney, bladder, ovaries, colon.

In gastric cancer, bevacizumab, a recombinant humanized monoclonal antibody targeting VEGF, has been investigated in a randomized phase III setting (AVAGAST trial [Avastin in gastric cancer]).[8] A significant benefit in progression free survival (PFS) and overall response rate (ORR) could been shown, but OS was not significantly improved. Ramucirumab, a specific anti-VEGF-R-2 antibody, was investigated in combination with first-line chemotherapy (5-FU, cisplatin) in patients with metastatic stomach or GEJ cancer in a double-blind, randomized, placebo-controlled phase 3 study (RAINFALL). Adding ramucirumab to first line chemotherapy did not show a benefit in OS in this patient cohort.[9] In the second line treatment of patients with advanced gastric or GEJ cancer, ramucirumab showed significant improvement in OS as monotherapy compared to BSC (phase III REGARD trial),[10] as well as in combination with chemotherapy (ramucirumab + paclitaxel vs paclitaxel monotherapy, phase III RAINBOW trial).[11] Based on these results, ramucirumab in combination with paclitaxel was approved for targeted second line treatment of advanced gastric or GEJ cancer.

The role of tyrosine kinase inhibitors (TKI's) which inhibit VEGF, VEGFR (vascular endothelial growth factor receptor) and EGFR (epidermal growth factor receptor) in metastatic or advanced gastric and GEJ cancer has been analyzed in combination with chemotherapy. Sorafenib, an oral inhibitor of raf tyrosine kinase and several receptor tyrosine kinases such as VEGF-2,3, PDGFR-ß, in combination with docetaxel and cisplatin showed promising results for OS and PFS rates (14.9 months, 90% confidence interval [CI] [8.6-15.2 months]; 5.8 months, 90% CI [5.4-7.2]).[12] In 52 patients with advanced chemorefractory gastric cancer, the effect of monotherapy with sunitinib, a multitargeted receptor tyrosine kinase inhibitor against the VEGF and PDGF family, was investigated in a phase II trial of the AIO with limited effect on tumor response, but good tolerability.[13] The activity of the oral multikinase inhibitor regorafenib was evaluated in refractory advanced gastric adenocarcinoma in an international randomized phase II trial (INTEGRATE), in which patients received at a 2:1 ratio BSC plus regorafenib (n = 97) vs placebo (n = 50). Regorafenib significantly prolonged PFS (2.6 months vs 0.9 months; hazard ratio [HR] 0.4, 95% CI 0.28-0.59, $P < .001$).[14] Pazopanib, an oral tyrosine kinase inhibitor, selectively inhibits VEGFR-1, -2, -3, c-kit and PDGF in tumors with overexpression of these receptors resulting in inhibition of tumor angiogenesis. Fast bioavailability can be achieved by oral intake. Monotherapy of pazopanib has already been investigated in different tumor entities within clinical trials. Promising activity of pazopanib was observed in several phase II trials with tolerable toxicities in metastatic kidney cancer,[15] breast cancer,[16,17] soft tissue sarcoma,[18] and nonsmall cell lung cancer.[19] The toxicities related to pazopanib reported in these trials mainly comprised hypertension, liver toxicity, diarrhea, vomiting and fatigue. Based on the results of a phase III trial with pazopanib monotherapy in patients with locally advanced or metastatic kidney cancer, pazopanib monotherapy was approved in the United States (2009) and Europe (2010) for this tumor entity. The study showed a significant prolongation of PFS with pazopanib vs placebo.[20]

The combination of pazopanib with chemotherapy was investigated in colorectal cancer with the combination of pazopanib with FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) or CAPOX (capecitabine/oxaliplatin).[21]

In our trial, we aimed to transfer the beneficial therapeutic effects of antiangiogenesis into a well-tolerated first line regimen. We therefore investigated the effect of the combination therapy of pazopanib plus FLO (5-fluorouracil, folinic acid, oxaliplatin) vs FLO alone in patients with advanced gastric and GEJ cancer. A dose-finding study with FLO was not necessary as FOLFOX and pazopanib were well tolerable in the phase I trial in colorectal cancer.[21]

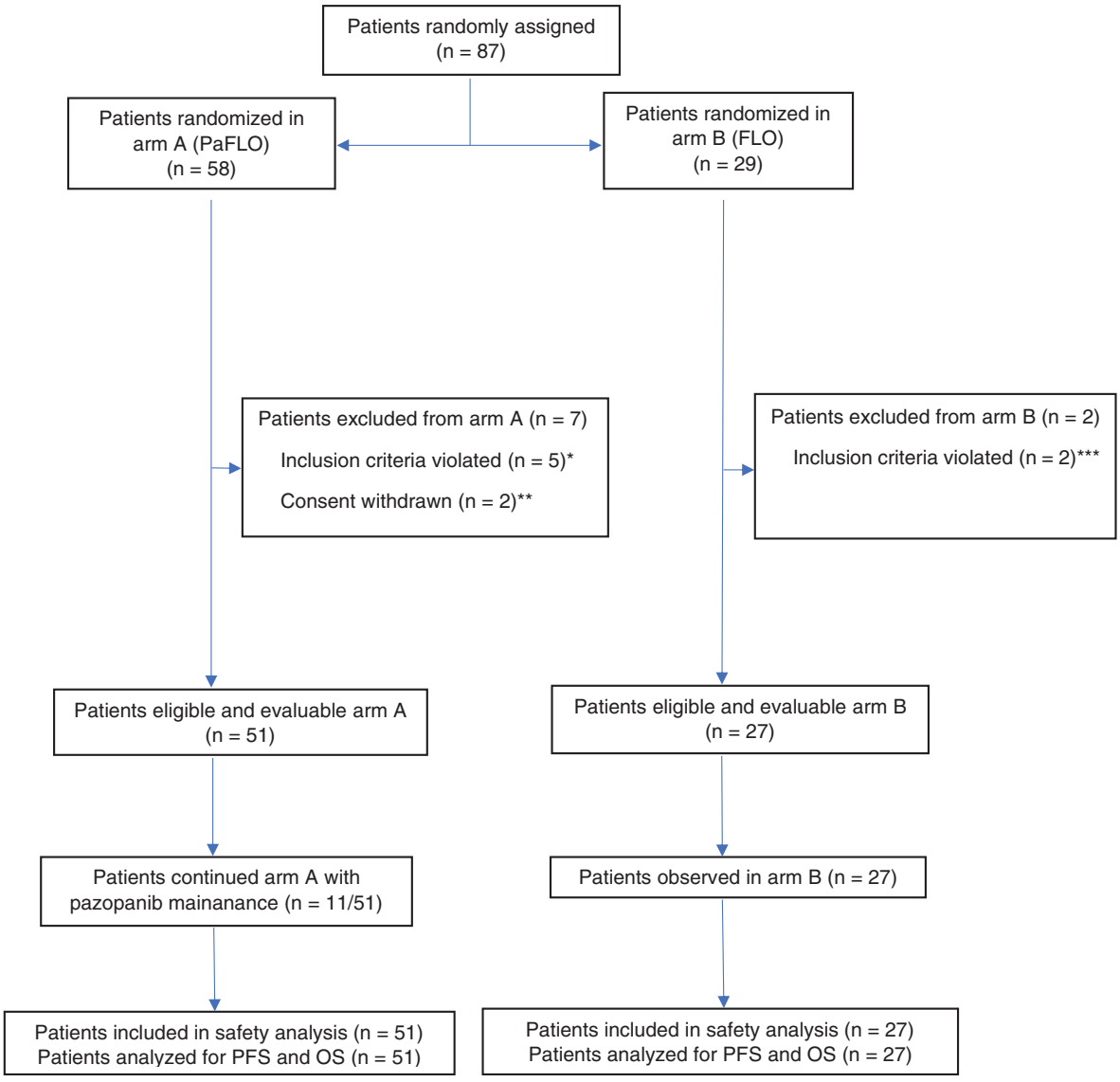
2 | MATERIALS AND METHODS

2.1 | Patient eligibility and group stratification

Eligible patients were aged ≥18 years with histologically confirmed adenocarcinoma of the stomach or GEJ with either metastatic or locally advanced disease not amenable for curative resection. Additional eligibility criteria included no former chemotherapy (except for neoadjuvant/adjuvant prior therapy completed >6 months before randomization), at least one unidimensionally measurable tumor lesion (RECIST v. 1.1), as well as adequate hematologic, hepatic, renal and metabolic functional parameters and Eastern Co-operative Oncology Group performance status (ECOG) ≤ 2. Exclusion criteria included Her2neu (human epidermal growth factor receptor 2) overexpression, known hypersensitivity against 5-FU, folinic acid, oxaliplatin (or other platin-derivates) or pazopanib, clinical evidence or proven central nervous system metastases or meningeosis carcinomatosa, second malignancy ≤ 5 years prior to randomization (except for in situ carcinoma of the cervix and basal-cell carcinoma of the skin treated in curative approach), peripheral neuropathy NCI grade > 1, history of GI bleeding or malabsorption, as well as uncontrolled acute infection (see trial synopsis in the Supporting Information).

2.2 | Treatment plan

The study was designed as open-label randomized multicenter phase-II trial for first line therapy of patients with advanced adenocarcinoma of the stomach or GEJ and randomized 2:1 either in arm A with combination of pazopanib and FLO (PaFLO) or arm B with FLO mono therapy. In arm A, intravenous 5-FU was administered with 2600 mg/m^2 over 24 hours, leucovorine 200 mg/m^2 over 2 hours, oxaliplatin 85 mg/m^2 over 2 hours on day one every 2 weeks for 12 cycles and oral pazopanib 800 mg/m^2 once daily, simultaneously to FLO and continued as monotherapy (maintenance) until progression. In arm B, FLO monotherapy on day one was administered in respective doses every 2 weeks for 12 cycles followed by clinical observation (see trial synopsis in the Supporting Information). According to local standard, antiemetic medication



* n = 5: No measurable lesion

**n = 2: Consent withdrawn prior to first treatment

***n = 1: No measurable lesion, n = 1: Carcinoma of different origin: pancreas

FIGURE 1 Consort diagram. Overview of randomly assigned patients and patients included in final analysis. FLO, 5-fluorouracil, folinic acid, oxaliplatin; OS, overall survival; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin; PFS, progression-free survival [Color figure can be viewed at wileyonlinelibrary.com]

prior and during therapy cycles was given. Patients from 20 national clinical centers were included. The trial was designed by the Charité Comprehensive Cancer Center and the AIO.

2.3 | Measures of outcomes

The primary endpoint of the study was the progression-free survival rate (PFSR) at 6 months. Secondary endpoints included the PFSR after 9 and 12 months, the PFS, response rate, duration of response, toxicities, tolerability, OS and time to treatment failure.

2.4 | Assessment of toxicity, safety and efficacy

The assessment of toxicity was performed according to CTC AE vs 3.0. The safety analysis included all treatment associated and independent adverse events. The PaFLO trial was performed as a 2:1

TABLE 1 Baseline characteristics of patients

	Arm A (PaFLO, n = 51)	Arm B (FLO, n = 27)
Sex		
Male	37 (72%)	17 (63%)
Female	14 (27%)	10 (37%)
Age (years)		
Median	65	60
ECOG		
0	22 (43%)	12 (44%)
1	26 (51%)	13 (48%)
2	3 (6%)	2 (7%)
Site of tumor		
AEG	30 (59%)	8 (30%)
Stomach	21 (41%)	19 (70%)
Histological type (Laurén)		
Intestinal	15 (30%)	9 (33%)
Diffuse	8 (16%)	6 (22%)
Mixed	6 (12%)	1 (3.7%)
Not specified	19 (37%)	10 (37%)
WHO classification		
Mucinous	1 (2%)	1 (4%)
Tubular	6 (12%)	3 (11%)
Signet ring cells	9 (18%)	8 (30%)
Not specified	26 (51%)	12 (44%)
Clinical stage (T), UICC version 7.0		
uT1	5 (10%)	1 (4%)
uT2	3 (6%)	0 (0%)
uT3	14 (29%)	11 (44%)
uT4	10 (21%)	4 (16%)
uT4a	1 (2%)	1 (4%)
Tx	13 (27%)	8 (32%)
Lymphonodal stage (N), UICC version 7.0		
N0	2 (4%)	1 (4%)
N1	10 (21%)	7 (28%)
N2	6 (12%)	1 (4%)
N3	11 (23%)	7 (28%)
N+	–	2 (8%)
Nx	14 (29%)	7 (28%)
Metastatic spread (M), UICC version 7.0		
M0	3 (6%)	0 (0%)
M1	48 (94%)	27 (100%)
No. organs involved		
1	1 (2%)	2 (7%)
2	14 (27%)	11 (41%)
≥3	36 (71%)	14 (51%)
Type of operation		
Esophagectomy	2 (18%)	0 (0%)
Gastrectomy	9 (82%)	6 (100%)
Local recurrence		
Yes	9 (18%)	5 (18%)
No	42 (82%)	22 (81%)

Abbreviations: AEG, adenocarcinoma of the esophago-gastric junction; ECOG, Eastern Co-operative Oncology Group; FLO, 5-fluorouracil, folinic acid, oxaliplatin; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin; UICC, union internationale contre le cancer; WHO, world health organization.

randomized phase II trial. The standard arm (FLO without pazopanib) served as internal control to avoid selection bias. Between the two arms no formally statistical comparison was planned. For the statistical analysis and sample size calculation PFS was defined as time from randomization to either first disease progression or death from any cause. Censored patients were alive at time of analysis and were censored at date of last disease assessment. OS was measured from date of randomization to date of death from any cause.

2.5 | Statistical analysis

For the sample size calculation, the Simon's two-stage design was used. According to the data of the ToGA trial, a randomized phase III trial, an estimated medium PFSR of 40% at 6 months was reached with a cisplatin/fluoropyrimidine combination.[2] In a randomized phase III trial using FLO as first line treatment a PFSR at 6 months of 44% was reached.[6] Based on these data we estimated a PFSR at 6 months of 40% as a minimum to be reached with the FLO combination (null-hypothesis) and expected a PFSR of 55% in the experimental arm (PaFLO). At an alpha error of 0.10 and beta error of 0.20 (power of 80%, respectively), according to Simon's two-stage design, 30 eligible and evaluable patients were treated in the experimental PaFLO arm, in the first step. As ≥12 patients had no progression after 6 months, the second recruiting step was performed with further enrollment of 20 eligible and evaluable patients. According to this model, a total of 75 eligible (without major violation of inclusion criteria) and evaluable (at least one dose of treatment received) patients had to be recruited, 50 in the experimental and 25 in the control arm. The FLO arm served as internal control as calibration arm without preplanned comparisons between the two arms. Therefore, all comparisons are of exploratory nature. The estimation of survival rates was performed according to Kaplan-Meier analysis. Statistical comparison analysis applied the log-rank test and the proportional hazard model. All tests are two-sided following the 5% level of significance using SPSS 27.0 (SPSS, Inc, Chicago, IL).

3 | RESULTS

Between December 2011 and July 2014, 87 patients were enrolled. Seventy-eight patients were eligible and evaluable for safety and efficacy analysis, 51 in arm A (PaFLO) and 27 in arm B (FLO), (Figure 1). Baseline patient characteristics are shown in Table 1. The median age was 65 years in the PaFLO-arm and 60 years in the FLO-arm. In both therapy arms, the majority of patients were male (n = 37 PaFLO, n = 17 FLO) and had a performance status of ECOG 1. According to Lauren's classification, the histological type of intestinal adenocarcinomas constitutes the majority of tumors in both therapy arms. 94% of patients in the PaFLO arm and 100% in the FLO arm had metastatic disease, the remaining 3 patients in the PaFLO arm had locally advanced

TABLE 2 Overview of adverse events

	Arm A (PaFLO, n = 51)					Arm B (FLO, n = 27)				
Grade	**0**	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Hematologic										
Leucopenia	35 (69%)	4 (8%)	9 (18%)	3 (6%)	–	24 (89%)	2 (7%)	1 (4%)	–	–
Neutropenia	31 (61%)	5 (10%)	3 (6%)	11 (22%)	1 (2%)	24 (89%)	2 (7%)	–	1 (4%)	–
Thrombocytopenia	36 (71%)	11 (22%)	3 (6%)	1 (2%)	–	23 (85%)	3 (11%)	1 (4%)	–	–
Anemia	36 (71%)	6 (12%)	8 (16%)	1 (2%)	–	19 (70%)	5 (18%)	–	3 (11%)	–
Nonhematologic										
Fever (without neutropenia)	42 (82%)	5 (10%)	–	4 (8%)	–	25 (93%)	1 (4%)	1 (4%)	–	–
Nausea	16 (31%)	19 (37%)	8 (16%)	8 (16%)	–	10 (37%)	11 (41%)	6 (22%)	–	–
Loss of appetite	23 (45%)	17 (33%)	6 (12%)	5 (9%)	–	14 (52%)	4 (15%)	7 (26%)	–	2 (7%)
Vomiting	27 (53%)	16 (31%)	5 (10%)	3 (6%)	–	15 (56%)	5 (18%)	5 (18%)	2 (7%)	–
Diarrhea	23 (45%)	21 (41%)	8 (12%)	1 (2%)	–	16 (60%)	7 (26%)	2 (7%)	2 (7%)	–
Obstipation	31 (61%)	19 (37%)	1 (2%)	–	–	20 (74%)	4 (15%)	3 (11%)	–	–
Mucositis	39 (76%)	10 (20%)	2 (4%)	–	–	22 (81%)	4 (15%)	1 (4%)	–	–
Fatigue	24 (47%)	15 (29%)	8 (16%)	4 (8%)	–	14 (52%)	6 (22%)	6 (22%)	–	1 (4%)
Alopecia	33 (65%)	18 (35%)	–	–	–	22 (81%)	3 (11%)	1 (4%)	1 (4%)	–
Alteration of nails	43 (84%)	8 (16%)	–	–	–	26 (96%)	1 (4%)	–	–	–
Hand-foot syndrome	40 (78%)	8 (16%)	2 (4%)	1 (2%)	–	25 (93%)	2 (7%)	–	–	–
Change in taste	34 (67%)	13 (26%)	4 (8%)	–	–	23 (85%)	3 (11%)	1 (4%)	–	–
Vision disorders	45 (88%)	5 (10%)	1 (2%)	–	–	24 (89%)	2 (7%)	1 (4%)	–	–
Hearing impairment	49 (96%)	2 (4%)	–	–	–	27 (100%)	–	–	–	–
Peripheral neuropathy	13 (26%)	22 (43%)	12 (23%)	3 (6%)	1 (2%)	9 (33%)	9 (33%)	7 (26%)	2 (7%)	–
Vertigo	41 (80%)	7 (14%)	3 (6%)	–	–	24 (89%)	2 (7%)	1 (4%)	–	–
ALT	42 (82%)	3 (6%)	1 (2%)	5 (10%)	–	26 (96%)	1 (4%)	–	–	–
AST	43 (84%)	3 (6%)	1 (2%)	4 (8%)	–	25 (93%)	2 (7%)	–	–	–
Increase of creatinine	49 (96%)	2 (4%)	–	–	–	26 (96%)	1 (4%)	–	–	–
Bilirubin direct	42 (82%)	2 (4%)	–	1 (2%)	–	23 (85%)	–	–	–	–
Bilirubin total	47 (92%)	1 (2%)	1 (2%)	2 (4%)	–	27 (100%)	–	–	–	–

Abbreviations: FLO, 5-fluorouracil, folinic acid, oxaliplatin; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin.

tumors not amenable to a curative approach. The majority of patients had 3 or more organs involved (71% PaFLO arm, 51% FLO arm). Prior esophagectomy or gastrectomy was performed in 11 patients in the PaFLO arm (esophagectomy n = 2 [18%], gastrectomy n = 9 [82%]) and in 6 patients of the FLO arm (gastrectomy n = 6 [100%]). Local recurrence of disease was observed in 18% of patients in arm A and B (arm A: n = 9, arm B: n = 5).

The median number of cycles of FLO chemotherapy administration was 8 in both therapy arms. Dose reduction of chemotherapy was similar in both arms (37% PaFLO arm, 33% FLO arm). The dose of pazopanib had to be reduced in 11 of 51 patients (22%). In 9 of 11 patients, dose was reduced once (to 600 mg), in 2 of 11 patients dose was reduced twice (to 400 mg). Dose interruption of pazopanib was necessary in 45 of 51 patients (88%). The median time of dose interruption was 6 days (range, 1-80).

TABLE 3 Efficacy

	Arm A (PaFLO, n = 51)	Arm B (FLO, n = 27)
Best response confirmed		
CR	1 (2%)	1 (4%)
PR	12 (23%)	6 (22%)
SD	24 (47%)	9 (33%)
PD	9 (18%)	9 (33%)
DCR (CR + PR + SD)	37 (72%)	16 (59%)
ORR (CR + PR)	13 (25%)	7 (26%)

Abbreviations: CR, complete response; DCR, disease control rate; FLO, 5-fluorouracil, folinic acid, oxaliplatin; ORR, overall response rate; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin; PR, partial response; SD, stable disease.

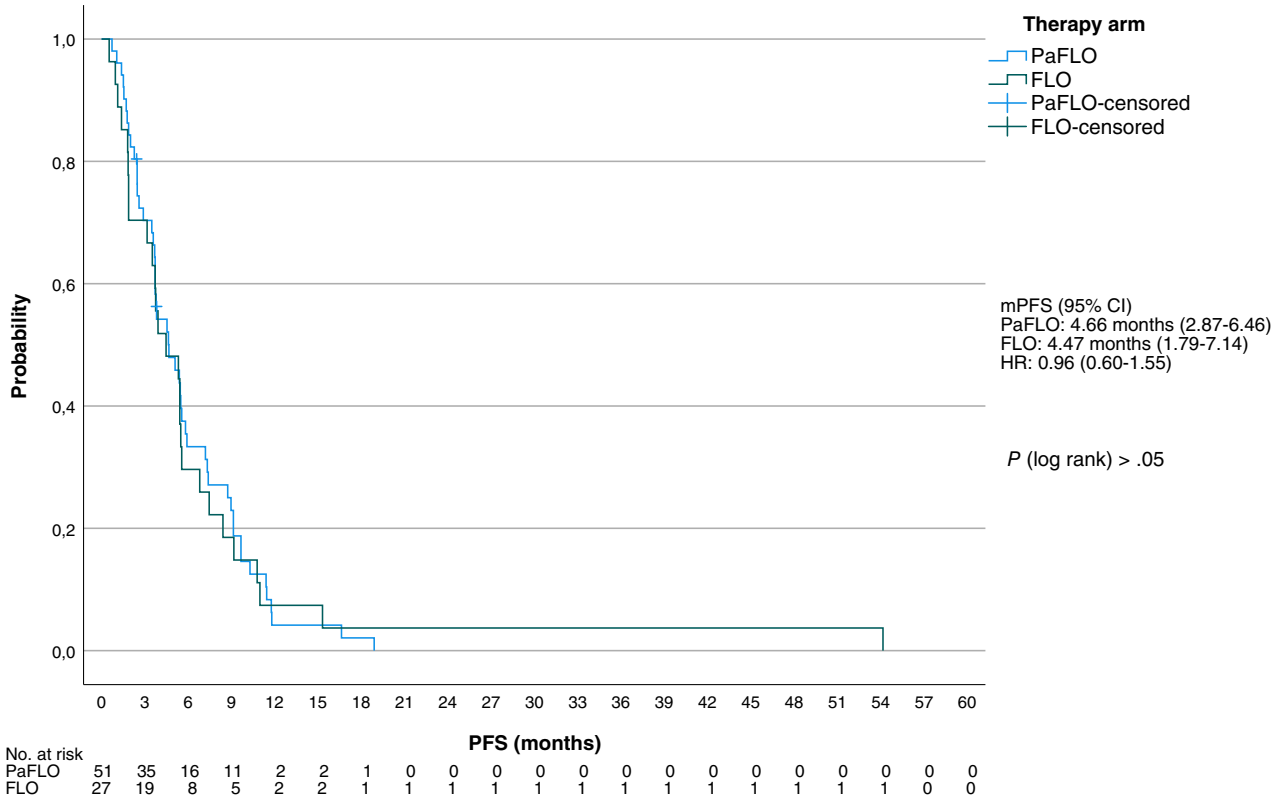


FIGURE 2 Kaplan-Meier curve of progression-free survival for all eligible and evaluable patients. FLO, 5-fluorouracil, folinic acid, oxaliplatin; HR, hazard ratio; mPFS, median progression free survival; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin; PFS, progression-free survival

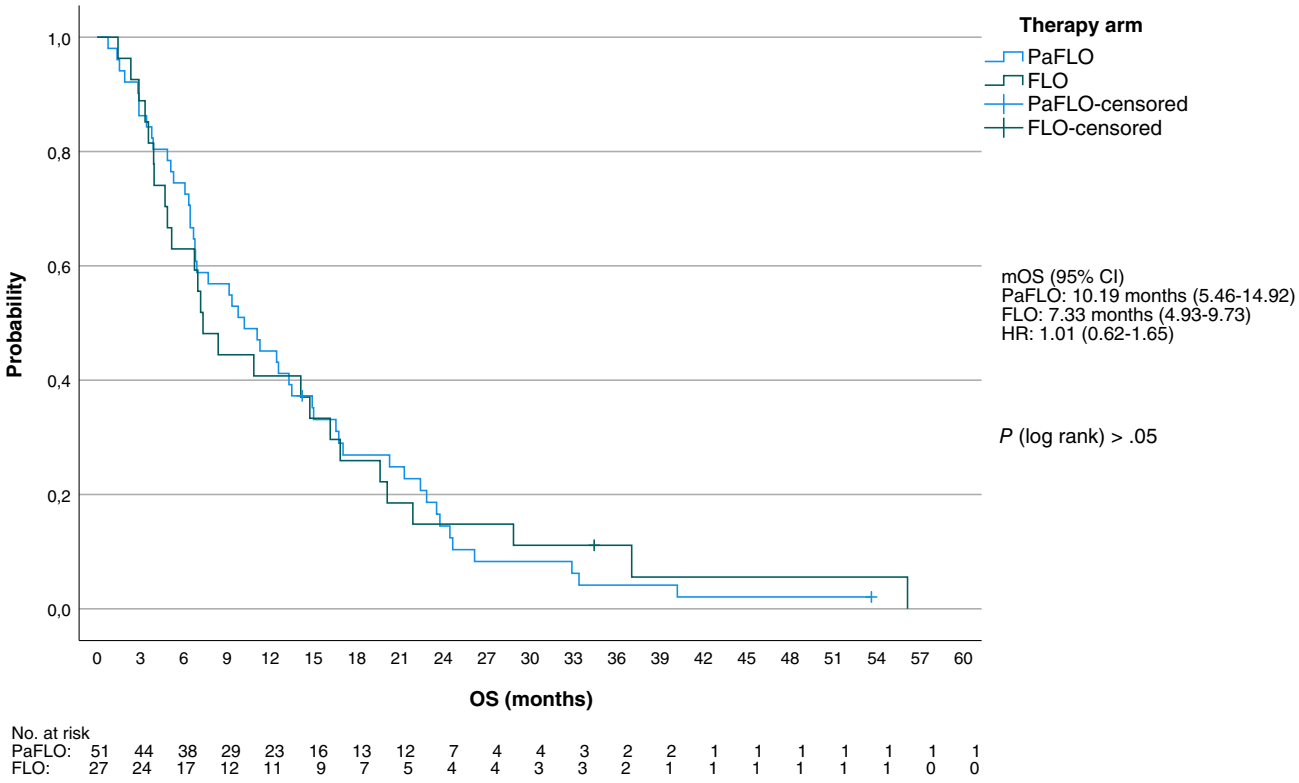


FIGURE 3 Kaplan-Meier curve of overall survival of all eligible and evaluable patients. FLO, 5-fluorouracil, folinic acid, oxaliplatin; HR, hazard ratio; mOS, median overall survival; OS, overall survival; PaFLO, pazopanib plus 5-fluorouracil, folinic acid, oxaliplatin

The main adverse events are presented in Table 2. In descending order, adverse events mainly comprised loss of appetite, nausea, fatigue, diarrhea, neutropenia as well as thrombocytopenia. With regard to CTC AE grade 3 toxicities, leading AE's were neutropenia (22%, n = 11), nausea (16%, n = 8), elevated ALT levels (10%, n = 5) and loss of appetite (9%, n = 5) in the PaFLO arm and anemia (11%, n = 3), vomiting (7%, n = 2), diarrhea (7%, n = 2), as well as peripheral neuropathy (7%, n = 2) in the FLO arm. Grade 4 toxicity was reported only in 2 patients of the PaFLO arm (2% neutropenia (n = 1), 2% peripheral neuropathy (n = 1) and 3 patients in the FLO arm (7% loss of appetite [n = 2], 4% fatigue [n = 1]). Overall, there were 61 serious adverse events (SAE's) reported, 47 in the PaFLO arm and 14 in the FLO arm. Taking the 2:1 randomization into account, there still seem to be slightly more SAE's in the PaFLO group. Seven SAE's in the PaFLO group occurred due to increase of ALT-/AST-, Bilirubin values related to pazopanib. Each event was causally associated with study medication (rating "possible", "probable", "definite"). After assessment of the coordinating investigator and independent data monitoring committee, there were no safety-relevant considerations concerning study continuation.

In the efficacy analysis (Table 3), PaFLO proved to be effective and well tolerated. There were no major differences in efficacy between PaFLO compared to FLO. Median PFS was 4.66 months in the PaFLO arm vs 4.47 months in the FLO arm (HR 0.96, 95% CI 0.60-1.55, $P = .882$ [exploratory]). Median OS was 10.19 months (PaFLO) vs 7.33 months (FLO; HR 1.01, 95% CI 0.62-1.65, $P = .953$ [exploratory]). After 6 months, the PFS rate was 34% in the PaFLO arm vs 30% in the FLO arm, after 9 months 27% vs 18% and after 12 months 4% vs 7%. Complete response was 2% in the PaFLO arm (n = 1) vs 4% (n = 1) in the FLO arm. The overall response rate was 25% (n = 13, PaFLO) vs 26% (n = 7, FLO). Stable disease was documented in 24 patients of the PaFLO arm and 9 patients of the FLO arm. The disease control rate was 72% (n = 37) with PaFLO vs 59% (n = 16) with FLO therapy. Nine patients of each therapy arm showed progressive disease (18% PaFLO arm, 33% FLO arm). Results of efficacy analysis of all eligible and evaluable patients are presented in Table 3 and Figures 2 and 3 (Kaplan-Meier curves).

4 | DISCUSSION

The aim of this open label phase II trial was to investigate the efficacy of the combination of the tyrosine kinase inhibitor pazopanib in combination with FLO chemotherapy in patients with advanced adenocarcinoma of the stomach and GEJ in the first line setting. Our results show good feasibility of pazopanib with median number of chemotherapy (FLO) cycles of 8 in each arm. Dose reduction of chemotherapy was only 37% in the PaFLO arm vs 33% in the FLO arm. Pazopanib had to be reduced overall in 23% of patients. The combination therapy of pazopanib and FLO showed good tolerability in patients in comparison with FLO monotherapy. The extent of adverse events possibly related to pazopanib in our trial was small and consistent with the toxicity data for pazopanib.[20] PaFLO resulted in a promising disease control rate of 72%, compared to 59% in the FLO arm. The median OS was numerically higher in the PaFLO arm compared to FLO (10.19 months vs 7.33 months). Despite these promising signs of efficacy of adding pazopanib, when comparing other efficacy parameters to the internal control arm this benefit seems to be small. The rate of patients without progression at 6 months was 34% in the PaFLO arm and 30% in the FLO arm. In the ToGA trial,[2] the PFS rate at 6 months was 40% and it was 44% in another AIO study.[6] The Kaplan-Meier curves show no consistent sign of separation. Comparing our PFS rate reached in this trial with the literature both arms (PaFLO and FLO) underperformed. The PFS rates are lower than expected in both arms. A possible explanation might be that in Germany a triple combination as first line (FLOT) was quite popular so that there might have been a bias to include patients in this trial who were a little bit more frail and did not qualify for a triple chemotherapy.

Overall, the addition of pazopanib to FLO showed signals of improved efficacy, but no major improvement could be detected.

Recent studies indicate that pharmacologic blockade of tumor angiogenesis plays a key role in inhibition of cancer growth and metastasis, reflecting a promising approach in antitumor therapy.

Several clinical trials investigated different antiangiogenic agents in advanced gastric cancer in view of efficacy and safety.[22] In second-line treatment of patients with advanced gastric/GEJ cancer with progression after first line therapy, the effect of the VEGFR-2 inhibitor ramucirumab was investigated in an international randomized phase III study (REGARD trial) compared to BSC. Ramucirumab administration significantly prolonged OS in 335 patients (median OS 3.8 months vs 5.2 months; $P = 0{,}047$, HR = 0,78, 95% CI 0.603-0.998).[10] The RAINBOW trial, an international randomized phase III trial, investigated the effect on OS of the combination of ramucirumab plus paclitaxel in 665 patients with advanced adenocarcinoma of the stomach or GEJ. The patients were randomized in a 1:1 ratio receiving either ramucirumab plus paclitaxel or placebo plus paclitaxel. The combination therapy of ramucirumab plus paclitaxel improved median OS from 7.4 to 9.6 months ($P = .017$, HR 0.807, 95% CI 0.678-0.962).[11] Based on these results, the combination of ramucirumab plus paclitaxel developed as a standard therapy for second line therapy of these patients.

In the first-line setting, the effect of ramucirumab vs placebo plus cisplatin and capecitabine/5-fluorouracil was investigated in a double-blind, randomized phase III trial (RAINFALL). The investigator-assessed PFS was significantly longer in the ramucirumab group compared to the placebo group (mPFS 5.7 months vs 5.4 months, $P = .016$, HR 0.753, 95% CI 0.607-0.935). However, a sensitivity analysis by a central independent radiological image analysis did not confirm the investigator's results of PFS ($P = .74$, HR 0.961, 95% CI 0.768-1.203). In the OS analysis, there was no difference in adding ramucirumab to chemotherapy in the first line setting.[9] The combination of ramucirumab plus cisplatin/capecitabine or 5-fluorouracil was not beneficial in this patient cohort.

Bevacizumab, a monoclonal antibody inhibiting VEGF and consequently tumor angiogenesis, showed significant benefit in PFS and ORR in 387 patients with administration of bevacizumab vs placebo combined with cisplatin plus capecitabine (AVAGAST trial). Especially non-Asian patients seemed to benefit from this combination therapy. However, the primary endpoint OS was not reached in the study.[23]

The role of combination of the tyrosine kinase inhibitor pazopanib in combination with chemotherapy was investigated in a prospective phase II trial of pazopanib plus CAPOX in previously untreated Asian patients with advanced gastric cancer. In the single arm trial, 66 Asian patients received pazopanib plus CAPOX every 3 weeks. The primary endpoint, ORR, was 62.4%. Stable disease was documented in 23 patients (34.8%), resulting in a 92.4% disease control rate. Median PFS and OS were 6.5 months (95% CI 5.6-7.4) and 10.5 months (95% CI 8.1-12.9), respectively. Thirty-four patients (51.5%) experienced a treatment-related toxicity of grade three and more. All in all, the combination of pazopanib and CAPOX showed a moderate effect in these patients and was well tolerable.[24]

The results of our trial, adding pazopanib to FLO in a randomized phase II design, integrate well into the current knowledge. Signs of efficacy could be detected which were not indicative of any statistical major improvement. Compared to the Asian single arm design,[24] the randomized design of our trial using a calibration arm FLO puts the added benefit of pazopanib into a more realistic perspective.

So far, all trials investigating antiangiogenic treatment in the first line setting of gastric cancer have failed (RAINFALL, AVAGAST).[9,23] The same is true for investigating VEGF-inhibition in the perioperative setting STO3 trial.[25] There are speculations that there might be a still unknown biologic reason that VEGF-inhibition in gastric cancer is more active in more advanced disease.

Limitations of our trial are obviously the small sample size. Although 78 eligible and evaluable patients are an adequate number for a randomized phase II trial, this small number can only show major activity signals and might miss smaller amounts of benefit. Our trial might show promising signs of efficacy of pazopanib but not enough to support this combination in future trials.

In our patient cohort of the PaFLO arm, the majority of patients (59%, n = 30) suffered from GEJ cancer and 41% (n = 21) of the patients from gastric cancer. In contrast, patients in the FLO arm mainly had gastric cancer (70%, n = 19) and 30% (n = 8) of patients had GEJ cancer. As predictions from the nomogram illustrate, patients with GEJ cancer show a worse outcome compared to gastric cancer. The estimated disease-specific survival (DSS) demonstrates a 5-year survival rate of ~0.96 in patients with gastric cancer compared to ~0.91 in patients with GEJ cancer.[26,27] The higher proportion of GEJ cancer patients in the PaFLO arm compared to the FLO arm might therefore have an unfavorable effect on OS in the PaFLO arm. This might have a small negative influence for the overall result of adding pazopanib to chemotherapy, showing no major improvement in this trial. With respect to the number of organs involved at time of study entry, patients in the PaFLO arm have a higher extent of disease with 71% of patients (n = 36) with more than three organs involved compared to 15% (n = 14) in the FLO arm. This imbalance is unfavorable for the experimental patient cohort of the combinational PaFLO arm. Both, the predominance of the potentially worse GEJ cancer patients and the higher number of involved organs in the PaFLO arm at time of randomization might possibly have a small influence on our result, the absent major improvement of combining pazopanib with chemotherapy on patients' survival.

Biomarker studies are needed to identify potential subgroups with benefit of pazopanib. Nevertheless, there are promising other combinations of VEGF-inhibition in gastric cancer. Combining VEGF- inhibitors with checkpoint-inhibitors shows promising signs of synergism.[28,29] The approval of immune checkpoint inhibitors enriches the therapeutic landscape of patients with esophagogastric cancer with access to immune therapy in all therapy lines. In esophageal cancer, the anti-PD-1 (programmed death receptor-1) antibody nivolumab is approved in adjuvant setting for patients with squamous cell cancer (SCC) and GEJ cancer based on the Checkmate-577 trial (EMA, FDA).[30] In the first-line therapy, the PD-1 inhibitor pembrolizumab is also approved for patients with SCC and GEJ (EMA, FDA; Keynote-590 trial).[31] In the second-line therapy, approvals for nivolumab (EMA, FDA; Attraction-03 trial)[32] and pembrolizumab (FDA; Keynote-181 trial)[33] were achieved for SCC patients with recurrent locally advanced or metastatic disease after prior lines of systemic therapy. In gastric and GEJ adenocarcinoma, the FDA approved nivolumab in the first-line setting for patients with advanced GEJ or gastric cancer (Checkmate-649 trial)[34] as well as pembrolizumab in combination with trastuzumab in patients with locally advanced unresectable or metastatic Her2-positive gastric or GEJ adenocarcinoma as first-line therapy (Keynote-811 trial).[35] Much progress has been made, but the benefit is limited to a subgroup of patients. This development further supports the idea of combining immune checkpoint inhibition, VEGF-inhibition and chemotherapy in order to simultaneously restore exhausted antitumor T-cell function.

5 | CONCLUSIONS

In this randomized phase II trial, the combination therapy of pazopanib and FLO in patients with advanced adenocarcinoma of the stomach/GEJ was well tolerable. Adding pazopanib to chemotherapy shows signs of added efficacy but no major improvement in this patient cohort. Further investigations are needed to clarify the role of potential predictive subgroups who may benefit most from pazopanib.

ACKNOWLEDGMENTS

We thank all patients who participated in this trial and all principal and subinvestigators and study centers for their successful collaboration. Pazopanib was kindly provided by GlaxoSmithKline and Novartis for our trial. We thank GlaxoSmithKline and Novartis for financial support of this investigator-initiated trial. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST

Salah-Eddin Al-Batran: AIO Studien gGmbH (Invited speaker, Personal), Bristol-Myers Squibb (Advisory Board, Invited Speaker, Personal, Research Grant, Institutional, Financial interest), Immutep (Advisory Board, Personal), Lilly (Advisory Board, Invited Speaker, Personal, Research Grant, Institutional, Financial interest), MacroGenics (Advisory Board, Personal), MCI Deutschland GmbH (Invited Speaker, Personal), MSD Sharp & Dohme (Advisory Board, Personal, Research Grant, Institutional, Financial interest), Institute of Clinical Cancer Research IKF at Northwest Hospital (Personal, CEO/founder), AstraZeneca (Research Grant, Institutional, Financial interest), Celgene (Research Grant, Institutional, Financial interest), Eurozyto (Research Grant, Institutional, Financial interest), Federal Ministry of Education and Research (Research Grant, Institutional, Financial interest), German Gancer Aid (Krebshilfe) (Research Grant, Institutional, Financial interest), German Resarch Foundation (Research Grant, Institutional, Financial interest), Hospira (Research Grant, Institutional, Financial interest), Immutep (Research Grant, Institutional, Financial interest), Ipsen (Research Grant, Institutional, Financial interest), Medac (Research Grant, Institutional, Financial interest), Roche (Research Grant, Institutional, Financial interest), Sanofi (Research Grant, Institutional, Financial interest), Vifor (Research Grant, Institutional, Financial interest); Jens T. Siveke: Research funding from Bristol-Myers Sqibb, Celgene, Roche outside of our study; honoraria for consulting or advisory role from AstraZeneca, Baxalta, Bayer, Bristol-Myers Sqibb, Celgene, Immunocore, Novartis; minor equity in FAPI Holding and Pharma15 (<3%) and membership of the Board of Directors for Pharma15 outside the submitted work; Arndt Vogel: Speaker, consultancy and advisory role: Amgen, Roche, Bayer, Sanofi, BMS, Lilly, Novartis, EISAI, AstraZeneca, Merck, Incyte, Ipsen, PierreFabre, MSD, Sirtex, BTG, Servier, Terumo; Peter Thuss-Patience: Honoraria for advisory role: Astellas, BMS, Lilly, Merck, MSD, Nordic, Pfizer, Roche, Teva, Research Grants: Merck, GSK, Novartis. All other authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The trial was approved by the ethic committees of the participating institutions and complied with good clinical practice guidelines and the Declaration of Helsinki. All participants signed an informed consent. The trial was registered at ClinicalTrials.gov, identifier NCT01503372.

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SUPPORTING INFORMATION

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How to cite this article: Högner A, Al-Batran S-E, Siveke JT, et al. Pazopanib with 5-FU and oxaliplatin as first line therapy in advanced gastric cancer: A randomized phase-II study—The PaFLO trial. A study of the Arbeitsgemeinschaft Internistische Onkologie AIO-STO-0510. *Int. J. Cancer*. 2022;150(6):1007-1017. doi:10.1002/ijc.33864