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Published in:
EClinicalMedicine

DOI (link to publication from Publisher):
10.1016/j.eclinm.2024.102521

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

TRIFLURIDINE/TIPIRACIL (FTD/TPI) with or without bevacizumab in previously treated patients with esophago-gastric adenocarcinoma, a randomised phase III trial

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eClinicalMedicine
2024;70: 102521
Published Online 8 March 2024
https://doi.org/10.1016/j.eclinm.2024.102521

Summary

Background Trifluridine-tipiracil has shown a survival benefit compared with placebo in patients with chemo-refractory metastatic esophago-gastric adenocarcinoma. We aimed to compare the efficacy of trifluridine-tipiracil plus bevacizumab vs trifluridine-tipiracil monotherapy in pre-treated patients with metastatic esophago-gastric adenocarcinoma.

Methods This investigator-initiated, open-label, randomized trial enrolled patients with metastatic esophago-gastric adenocarcinoma. The main inclusion criteria were patients with pre-treated metastatic esophago-gastric adenocarcinoma, and WHO performance status 0 or 1. Participants were randomly assigned (1:1) to receive oral trifluridine-tipiracil (35 mg/m^2 twice daily on days 1–5 and 8–12 every 28 days) alone or combined with bevacizumab (5 mg/kg on days 1 and 15) until progression, unacceptable toxicity, or patient decision to withdraw. Randomisation was stratified by sex and treatment line. The primary endpoint was investigator-evaluated progression-free survival. All analyses were based on intention to treat. This trial is registered with EudraCT, 2018-004845-18.

Findings From Oct 1, 2019, to Sept 30, 2021, 103 patients were enrolled and randomly assigned to trifluridine-tipiracil (n = 53) or trifluridine-tipiracil plus bevacizumab (n = 50). The clinical cut-off date was March 1st, 2023, after a median follow-up of 36.6 months. Median progression-free survival was 3.1 months (95% CI 2.0–4.3) in the trifluridine-tipiracil group vs 3.9 months (3.0–6.3) in the trifluridine-tipiracil plus bevacizumab group (hazard ratio 0.68, 95% CI 0.46–1.02; p = 0.058). The most frequent grade 3 or worse adverse event was neutropenia, observed in 26 (49%) patients in the trifluridine-tipiracil group vs 23 patients (46%) in the trifluridine-tipiracil plus bevacizumab group. At least one hospitalization was observed in 21 patients (40%) in the trifluridine-tipiracil group and 22 patients (44%) in the trifluridine-tipiracil plus bevacizumab group. No deaths were deemed treatment related.

Interpretation In patients with pre-treated metastatic esophago-gastric cancer, trifluridine-tipiracil plus bevacizumab, compared to trifluridine-tipiracil monotherapy, did not significantly prolong progression-free survival. The combination of trifluridine-tipiracil with bevacizumab was well tolerated without increase in severe neutropenia and no new safety signals.

Funding Servier, Roche.

Keywords: Gastroesophageal; Cancer; Metastatic; Trifluridine-tipiracil; Bevacizumab

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Research in context

Evidence before this study

Recently, bevacizumab was shown to be an excellent partner for trifluridine/tipiracil (FTD/TPI) in patients with chemorefractory, metastatic colorectal cancer both in terms of activity and safety, and we were therefore inspired to conduct the present investigator-initiated, randomised trial. We searched PubMed with the terms "metastatic esophago-gastric cancer", "TAS-102" or "trifluridine/tipiracil", and "bevacizumab" for prospective, clinical studies of combination therapy with FTD/TPI and bevacizumab in patients with metastatic esophago-gastric cancer, without date, language, or trial type restrictions. We did not identify any published trial evaluating the combination of FTD/TPI with bevacizumab.

Added value of this study

This randomised trial is, to our knowledge, the first trial to compare FTD/TPI monotherapy with FTD/TPI plus bevacizumab combination regimen in patients with pre-treated, metastatic esophago-gastric cancer.

Implications of all the available evidence

The Danish Lon-Gas trial is the first randomised trial to compare FTD/TPI to FTD/TPI plus bevacizumab in patients with pre-treated esophagogastric cancer. The addition of bevacizumab to FTD/TPI did not significantly prolong progression-free survival or overall survival.

Introduction

Esophago-gastric adenocarcinoma (EGA) is a leading cause of death from cancer, with more than one million new cases diagnosed worldwide in 2020 and almost 800,000 deaths.[1] For patients with metastatic EGA, the treatment of choice has for many years been combination chemotherapy with the goals to relieve symptoms, prevent or delay tumor progression, prolong survival, and improve quality of life.[2,3] In Western countries, a doublet regimen of fluoropyrimidine (F) and platinum (P) or triplet combination with taxane in selected cases, is considered first line standard therapy, with the addition of trastuzumab in HER2-positive cases.[2–5] Recently, check point inhibitors (CPI) in combination with FP have been approved for patients in the first line setting.[6,7] After progression on first line therapy, the prognosis is poor, with limited treatment options presently including irinotecan or taxanes ± ramucirumab depending on prior treatment and with comparable efficacy.[2] Trifluridine/tipiracil (Lonsurf) is an orally active drug composed of a thymidine analogue (trifluridine) and a thymidine phosphorylase inhibitor (tipiracil).[8] Trifluridine is the active antitumor component and, following entry into cancer cells, it is phosphorylated by thymidine kinase to form trifluridine triphosphate, which is incorporated directly into DNA in place of thymidine. This process results in the inhibition of cell proliferation and tumor growth. Trifluridine is rapidly metabolised by thymidine phosphorylase in the liver and gastrointestinal tract to inactive forms. The addition of tipiracil inhibits trifluridine degradation and increases the bioavailability. FTD/TPI is not metabolised by dihydropyrimidine dehydrogenase (DPD) and can therefore be administered in patients with a DPD deficiency.

FTD/TPI has been shown to increase survival in chemo-refractory metastatic colorectal cancer, and addition of bevacizumab increased efficacy considerably.[9–11]

FTD/TPI also significantly prolonged progression-free survival and overall survival in patients with metastatic EGA in third or later line compared to placebo,[12] although the improvement of median survival was modest. FTD/TPI is approved by European Medicines Agency as monotherapy for the treatment of gastro-esophageal adenocarcinoma in third or later line. We designed this randomised investigator-initiated trial (Lon-Gas) to evaluate whether addition of bevacizumab to FTD/TPI could improve efficacy compared with FTD/TPI monotherapy in pre-treated patients with metastatic EGA. An ongoing, translational part of this trial, where possible novel predictive and prognostic biomarkers will be examined, is not included in this publication.

Methods

Trial design

This nationwide, randomised, investigator-initiated, open-label phase 3 trial was conducted at the four oncology centres treating esophago-gastric cancer. We investigated the efficacy and tolerability of FTD/TPI with or without bevacizumab in patients with metastatic, pre-treated esophagogastric adenocarcinoma (mEGA). The protocol recommended treatment until progression, unacceptable toxicity, or patient's wish for ending treatment.

Trial population

Main inclusion criteria were age at least 18 years, histologically confirmed esophagogastric adenocarcinoma and previous (perioperative or palliative) treatment with combination chemotherapy with a fluoropyrimidine (5-FU, capecitabine or S-1) and a platinum (cisplatin, oxaliplatin, or carboplatin). Patients with HER2-positive disease should have received trastuzumab concurrent with combination chemotherapy. Other criteria were Eastern Cooperative Oncology Group (ECOG)

performance status (PS) score of 0 or 1 and acceptable organ function (bilirubin no higher than 1.5 times the upper limit of normal, calculated glomerular filtration rate above 30 mL/min, neutrophil cell count of at least 1.5×10^9 per L, and a platelet count of at least 100×10^9 per L). Major exclusion criteria were known CNS metastasis and any other condition, that in the investigator's opinion, might pose a risk to the patient or interfere with the trial objectives (known allergy or intolerance to FTD/TPI or bevacizumab, known infection, drainage of ascites or pleural effusion within four weeks, intestinal obstruction, uncontrolled diabetes, uncontrolled hypertension, unstable angina pectoris or acute myocardial infarction within 12 months, known HIV or hepatitis B or C, major surgery within four weeks).

Randomisation

Patients, who met the eligibility criteria, were randomly assigned (1:1) to receive either FTD/TPI monotherapy or FTD/TPI plus bevacizumab in randomly chosen (with 1/3 probability each) block sizes of two, four, or six. Data and randomisation were handled by Odense Patient data Explorative Network (https://open.rsyd.dk/), using REDCap database (http://www.project-redcap.org/). The data management system ensures compliance with current legislation and regulations on data handling and data safety. Randomisation was stratified by sex and treatment line (second-line vs third or later line).

Procedures

Before random assignment, all patients had a complete medical history and physical examination done, including blood tests and ECG. Patients assigned to monotherapy were treated with standard dose FTD/TPI 35 mg/m^2 orally twice daily on days 1–5 and 8–12 every 28 days. Patients assigned to combination therapy received similar dose FTD/TPI plus bevacizumab (5 mg/kg intravenously) on days 1 and 15 every 28 days. If dose reduction was needed during treatment because of adverse events, the dose of FTD/TPI was reduced in increments of 5 mg/m^2. A maximum of three dose reductions were permitted to a minimum dose of 20 mg/m^2 twice daily. If patients had unacceptable toxicities related to bevacizumab, treatment with FTD/TPI monotherapy could be continued according to protocol without bevacizumab. Dose reduction of bevacizumab was not recommended. In the case of treatment delay of FTD/TPI, bevacizumab administration was delayed as well. Prophylactic use of granulocyte colony-stimulating factor was not recommended, but optional in case of febrile neutropenia or delay in treatment administration due to neutropenia. Clinical evaluation was done prior to each treatment cycle, and CT scan was performed at baseline and after every second cycle to evaluate treatment response according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Adverse events were evaluated before each cycle and graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Nadir hematology was measured on day 14 on cycle one and two. All patients were followed for progression of disease and survival until the end of the trial. Based on the severity of the underlying disease, hospitalizations due to well-known side effects to chemotherapy or complications to the underlying disease as well as hospitalization or death due to progression were not reported as Serious Adverse Events (SAEs), but registered as SAE in the case report form.

Outcome

The primary endpoint was investigator-evaluated progression free survival (PFS) calculated from the date of randomisation to the first date of radiological or clinical progression, time till death, or censored on cut-off date. Secondary endpoints included overall survival (OS), investigator-evaluated disease control rate (DCR) defined as complete or partial response or stable disease for at least two months, according to RECIST 1.1, and toxicity. OS was defined from the day of randomisation until death due to any cause. Exploratory endpoints, evaluating the correlation between tumor markers and outcome, have not yet been analysed and will be reported elsewhere.

Statistics

Prior data indicate that the median PFS on FTD/TPI is 2.0 months,[12] but we hypothesized that it is 4.0 months in patients receiving FTD/TPI plus bevacizumab.[10] If the true median PFS for FTD/TPI monotherapy is 2.0 months, and the true median PFS for patients receiving FTD/TPI + bevacizumab is 4.0 months, we needed to include 48 patients in FTD/TPI monotherapy group and 48 patients in FTD/TPI plus bevacizumab group to be able to reject the null hypothesis that the experimental and control survival curves are equal with probability (power) of 0.9 and a type I error of 0.05. The Kaplan–Meier method was used to estimate PFS and OS for each treatment arm. Estimates of the treatment effect were expressed as hazard ratios using a stratified Cox proportional-hazards analysis, including 95% confidence intervals and compared by log-rank test. Patients were analysed according to intention-to-treat. Efficacy analysis for OS, RR and DCR were not preplanned with alpha error control. We used descriptive statistics for calculation of patient characteristics, side effects and disease control rate (DCR). DCR was calculated in all treated patients who were evaluable for response at baseline. Patients with missing post-baseline response assessments were considered non-evaluable. All analyses and the power calculation were performed using the statistical software package Stata (version 17).

Ethics

The trial was approved by the Danish Medicines Agency (EudraCT no 2018-004845-18) and the Ethics Committee of Capital Region (reference number H-19001247) and conducted in accordance with the Declaration of Helsinki and ICH GCP. All patients provided written informed consent before any trial procedure was carried out.

Role of funding source

The funders of the trial had no role in trial design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the trial and had final responsibility for the decision to submit for publication.

Results

Patient and disease characteristics

A total of 103 patients were included and randomised from Oct 1, 2019 to Sept 30, 2021 (Fig. 1). All patients were included in the intention-to treat analysis. Patients were randomly assigned to receive either FTD/TPI monotherapy (n = 53) or FTD/TPI plus bevacizumab (n = 50). All patients received the allocated treatment. Baseline characteristics were well balanced between treatment groups (Table 1). Median age was 64 years (IQR 57–71). The primary tumor was located in esophagus, GEJ and stomach in 41 (40%), 41 (40%) and 21 (20%) patients, respectively. At the cut-off date for the present efficacy and safety analyses of March 1, 2023, 3 (3%) of 103 patients were alive after a median follow-up of 36.6 months. No patients were lost to follow-up. Median (IQR) duration of treatment was 1.8 months (1.1–4.7) in the FTD/TPI group and 3.4 months (1.2–8.1) months in the combination group (Table 2). The median number of treatment cycles was 2 (IQR 2–5) for patients receiving FTD/TPI, and 4 (IQR 2–8) for patients receiving FTD/TPI plus bevacizumab. Main reason for discontinuation of therapy was progressive disease in both arms, with 45 patients (85%) receiving FTD/TPI and 42 patients (84%) in the FTD/TPI plus bevacizumab group. Three patients (6%) receiving FTD/TPI monotherapy and one patient (2%) in the combination group discontinued due to toxicity. Median overall relative dose intensity RDI (IQR) for FTD/TPI was 90% (55–100) for those in the monotherapy group and 88% (73–100) in the combination therapy group, and median relative dose intensity for bevacizumab was 100% (75–100).

Efficacy

Median PFS was 3.1 months (2.0–4.3) in the FTD/TPI group and 3.9 months (3.0–6.3) in FTD/TPI plus bevacizumab group (HR 0.68; (95% CI 0.46–1.02), p = 0.058) (Fig. 2). There was a numeric difference in PFS at 6 months (21% vs 38%) and at 12 months (4% vs 10%) in favor of FTD/TPI plus bevacizumab, however not reaching statistical significance. Median OS was 8.5 months (6.7–10.0) in the FTD/TPI group vs 9.3 months (6.9–10.4) in the FTD/TPI plus bevacizumab group (HR 0.91, (95% CI 0.62–1.35) (Fig. 3). For FTD/TPI monotherapy and FTD/TPI plus bevacizumab, respectively, 50 (94%) and 49 (98%) patients were evaluable for response (Table 4). All four non-evaluable patients had only baseline CT performed and were excluded from trial due to patient wish, toxicity, bleeding from primary tumor and general poor condition. Objective response was seen in one (2%) (95% CI 0%–10%) patient in the FTD/TPI monotherapy arm and in four (8%) (95% CI 2%–19%) patients in the combination arm. DCR was seen in 28 patients (53%) (95% CI 39%–67%) in the FTD/TPI monotherapy arm and in 33 patients (66%) (95% CI 51%–79%) in the combination arm.

Safety

The safety population included all 103 patients, as all patients received treatment. Adverse events are shown in Table 3. There was no appreciable difference in severe toxicity, defined as CTCAE grade 3 or higher. The most common adverse events leading to dose reductions or delays were hematological. Grade 3 or 4 adverse events occurred in 39 (74%) patients in the monotherapy group and in 33 (66%) in the FTD/TPI plus bevacizumab group. Grade ≥3 neutropenia occurred in 26 (49%) patients receiving FTD/TPI monotherapy and in 23 (46%) receiving FTD/TPI plus bevacizumab. Febrile neutropenia occurred in four (8%) patients in the monotherapy group and in five (10%) patients in the FTD/TPI plus bevacizumab group. G-CSF was applied in 17 patients (32%) in the FTD/TPI group and in 12 patients (24%) in the FTD/TPI plus bevacizumab group. Other events grade ≥3 included fatigue in two (4%) and five (10%) patients, respectively. Nausea occurred in three patients in each group (6%/6%). Dose reductions occurred in 11 patients (21%) in the FTD/TPI group and in 14 patients (28%) in the FTD/TPI plus bevacizumab group. Therapy was postponed in 35 patients in each group. SAEs, that all were due to hospitalisations, were observed in 21 patients (40%) in the FTD/TPI group and in 22 patients (44%) in the group receiving FTD/TPI plus bevacizumab. One patient in the combination arm with bevacizumab experienced venous thromboembolic event grade 3 with pulmonary embolus and renal vein thrombosis, possibly related to treatment. The patient was asymptomatic. All deaths were disease-related, no deaths were deemed treatment-related.

Discussion

The outcome of patients with pretreated metastatic esophago-gastric adenocarcinoma is very poor with an expected PFS of less than two months and survival of

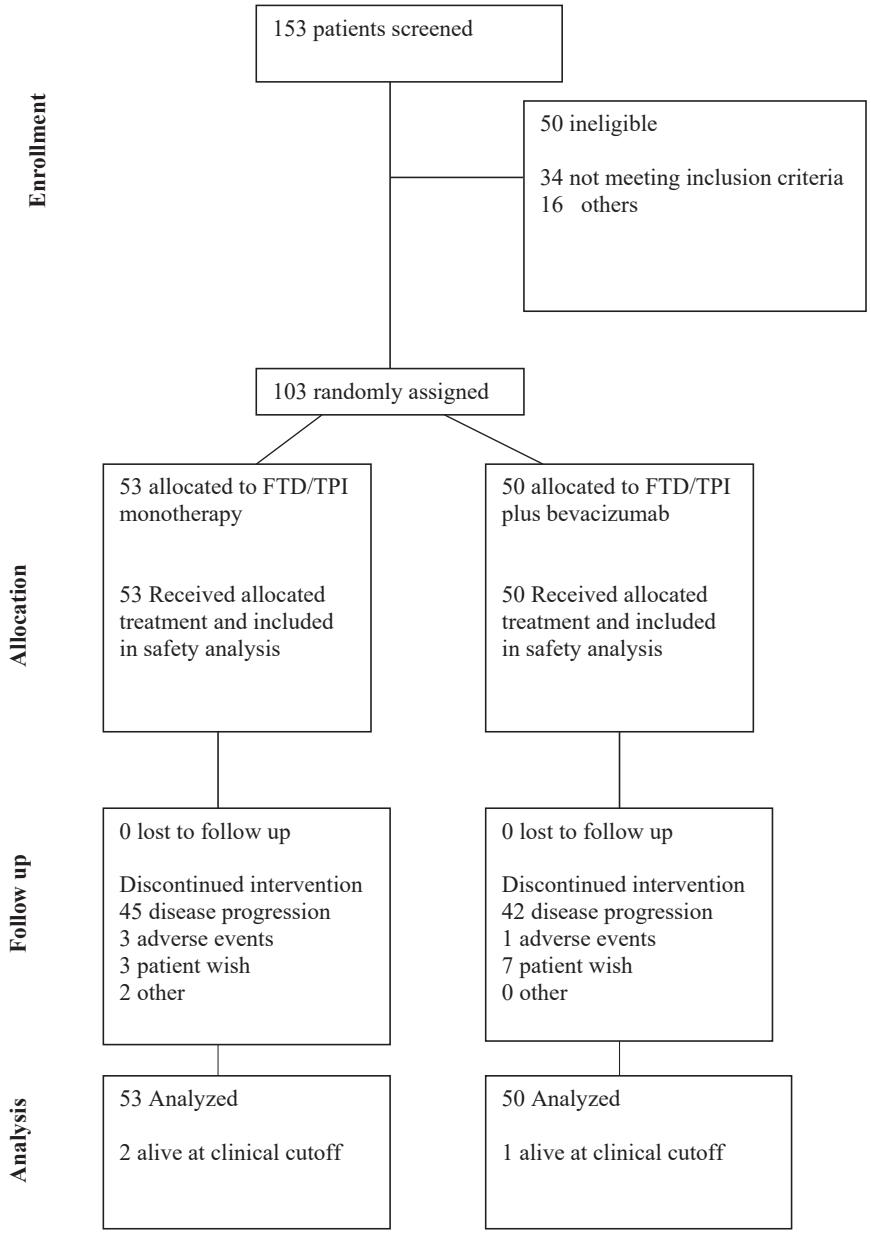

Fig. 1: Consort diagram.

three-four months.[13,14] Randomised studies have shown a modest, but significantly prolonged PFS and OS for second-line therapy.[13,15–18] Since the results of the German FLOT trial[19] became available, taxane-containing triplet combination therapy in the perioperative setting has emerged as a standard, and therefore many patients with recurrent disease have already been exposed to four to six months of combination chemotherapy including a taxane, and for these patients, treatment options are even more limited. More recently, check point inhibitors (CPI) in combination with chemotherapy, has been approved in the first line setting,[6,7] however this did not influence the Danish standard practice during the inclusion period in this trial.

Efficacy of CPI in second and later line treatment has been moderate.[20,21] In a large, primarily Asian phase III trial, nivolumab only slightly improved OS compared to placebo in third and later lines.[22] New effective treatment options for patients with pretreated, metastatic esophagogastric cancer still represent an unmet medical need.

	Trifluridine/tipiracil monotherapy (n = 53)	Trifluridine/tipiracil plus bevacizumab (n = 50)
Age (years)		
Median (IQR)	66 (61–71)	64 (56–71)
Sex		
Male	43 (81%)	39 (78%)
Female	10 (19%)	11 (22%)
WHO performance status		
0	25 (47%)	22 (44%)
1	28 (53%)	28 (56%)
Location primary tumour		
Esophagus	18 (34%)	23 (46%)
EGJ	22 (42%)	19 (38%)
Stomach	13 (24%)	8 (16%)
HER2 status		
HER2 negative	38 (72%)	31 (62%)
HER2 positive	15 (28%)	18 (36%)
Inconclusive	0	1
Number of metastatic sites		
Median (IQR)	2 (1–3)	2 (2–3)
Site of metastatic disease		
Liver	21	23
Lung	11	9
Lymph nodes	31	29
Peritoneum	6	9
Bone	6	4
Soft tissue	3	5
Other	7	7
Previous lines of therapy		
1	29 (55%)	27 (54%)
2	18 (34%)	21 (42%)
3	4 (7%)	2 (4%)
4	2 (4%)	0 (0%)
Prior systemic therapy for EGA		
Fluoropyrimidine (5-FU, capecitabine, S-1)	53 (100%)	50 (100%)
Platinum (cisplatin, oxaliplatin or carboplatin)	53 (100%)	50 (100%)
Taxane (docetaxel or paclitaxel)	37 (70%)	39 (78%)
Epirubicin	15 (28%)	7 (14%)
Irinotecan	7 (13%)	6 (12%)
Ramucirumab or bevacizumab	5 (9%)	0
Pembrolizumab	0	2 (4%)
Trastuzumab	15 (28%)	18 (36%)
Neutrophils elevated		
≥5 × 10^9/L	19 (36%)	25 (50%)
Platelets elevated		
≥400 (10^9/L)	4 (8%)	4 (8%)
Low albumin		
<35 g/L	16 (of 52 measured)	11 (of 49 measured)
Elevated alkaline phosphatase		
>100 U/L	26 (49%)	26 (52%)
Elevated lactate dehydrogenase		
>250 U/L	9 (17%)	9 (18%)
Elevated CRP		
>10 mg/L	16 (30%)	14 (28%)

Data are n (%), median (IQR). EGA, Esophago-gastric adenocarcinoma.

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

The TAGS trial demonstrated, that FTD/TPI significantly prolonged overall survival in patients with metastatic esophagogastric adenocarcinoma in third or later lines compared to placebo, with a 31% reduction in the risk of death with median OS prolonged from 3.6 to 5.7 months.[12]

In patients with chemo-refractory metastatic colorectal cancer, we have demonstrated that FTD/TPI plus bevacizumab, as compared with FTD/TPI monotherapy, was associated with a significant and clinically relevant improvement in progression-free and overall survival with minimal added toxicity,[10] and these results were recently confirmed in the SUNLIGHT trial, which showed an improvement in median overall survival of 3.3 months (HR 0.61; $p < 0.001$) and median progression-free survival of 3.2 months (HR 0.44; $p < 0.001$).[11] Bevacizumab is not approved in patients with metastatic EGA. However, a number of studies have demonstrated efficacy of anti-angiogenic therapy in patients with metastatic EGA in different lines of treatment.[23–26] Significantly improved PFS and RR, but not OS, were seen in the large first line phase III AVAGAST trial comparing chemotherapy plus bevacizumab vs chemotherapy alone.[23] Ramucirumab, a VEGFR2-receptor antibody, as monotherapy or in combination with paclitaxel, significantly prolonged OS in a pre-treated population and is recommended as a standard therapy.[14,27] Regorafenib, an oral multitargeted, anti-angiogenic, tyrosine kinase inhibitor, was shown to prolong PFS in a randomised phase II trial vs placebo,[25] and the subsequent phaseIII trial showed a modest improvement in OS from 4.0 to 4.5 months, HR 0.70 (95% CI 0.53–0.92).[26] However, neither regorafenib, ramucirumab nor FTD/TPI is approved in Denmark as standard of care. Another, potentially promising regimen combining FTD/TPI plus VEGF inhibition has been examined. In a pilot trial with 20 patients, tolerability and efficacy was evaluated with a combination of ramucirumab beyond progression with FTD/TPI. The combination was safe and with promising efficacy with PFS 2.9 months (95% CI 1.7–4.8) and OS 9.1 months (95% CI 5.4–10.1).[28] These results compare well with the results of the present trial. In another single-arm trial, the combination of FTD/TPI and ramucirumab showed a high DCR of 85% (95% CI 68–95) and PFS 5.9 months (95% CI 4.2–7.9) in a subgroup of 33 patients with no prior exposure to ramucirumab. These results were similar to the combination of paclitaxel and ramucirumab seen in a large, phase III trial,[27] but with a potentially more acceptable toxicity profile.[29] Also, of interest, in a prespecified subgroup analysis, higher response rates between 29% (95% CI 4–71) and 33% (95% CI 12–62) were found in the subgroup of patients previous treated with CPI.[29] A randomised trial of ramucirumab plus FTD/TPI vs ramucirumab plus paclitaxel is ongoing.[30]

In Lon-Gas, the primary endpoint of improved PFS was not met. Both PFS and OS in patients receiving

	Trifluridine/tipiracil monotherapy (n = 53)	Trifluridine/tipiracil plus bevacizumab (n = 50)
Duration of therapy		
Median, months (IQR)	1.8 (1.1–4.7)	3.4 (1.2–8.1)
Number of treatment cycles		
Total, median (IQR)	2 (2–5)	4 (2–8)
Number of FTD/TPI, median (IQR)	2 (2–5)	4 (2–8)
Bevacizumab, median (IQR)	–	4 (2–8)
Relative dose-intensity (RDI)		
Median RDI of FTD/TPI (IQR)		
RDI due to dose reduction	100% (65–100)	100% (91–100)
RDI due to delay	92% (80–100)	89% (77–100)
Overall RDI	90% (55–100)	88.% (73–100)
Bevacizumab		100% (75–100)
Reason for discontinuation		
Progression, RECIST + clinical, n (%)	41 + 4 (85%)	38 + 4 (84%)
Toxicity, n (%)	3 (6%)	1 (2%)
Patients wish, n (%)	3 (6%)	7 (14%)
Intercurrent death	0	0
Other	2 (4%)	0
Still on treatment as of data cut-off, n (%)	0	0

Data are n (%) unless otherwise indicated, median (IQR).

Table 2: **Treatment characteristics for 103 patients receiving trifluridine/tipiracil monotherapy or trifluridine/tipiracil plus bevacizumab.**

FTD/TPI monotherapy were longer than anticipated (mPFS 3.1 and mOS 8.5 months, respectively) compared to those of patients included in TAGS (PFS 2.0 and OS 5.7 months, respectively), thereby reducing the statistical power. In contrast to TAGS, which included heavily pretreated patients, in Lon-Gas only 24 (45%) patients in the FTD/TPI group and 23 (46%) patients in the FTD/TPI plus bevacizumab group had received two or more prior lines of therapy, including adjuvant, which may explain the longer PFS and OS in patients receiving FTD/TPI monotherapy in our trial as compared to the TAGS trial.

Of interest, the median duration of treatment was almost twice as long in the FTD/TPI plus bevacizumab

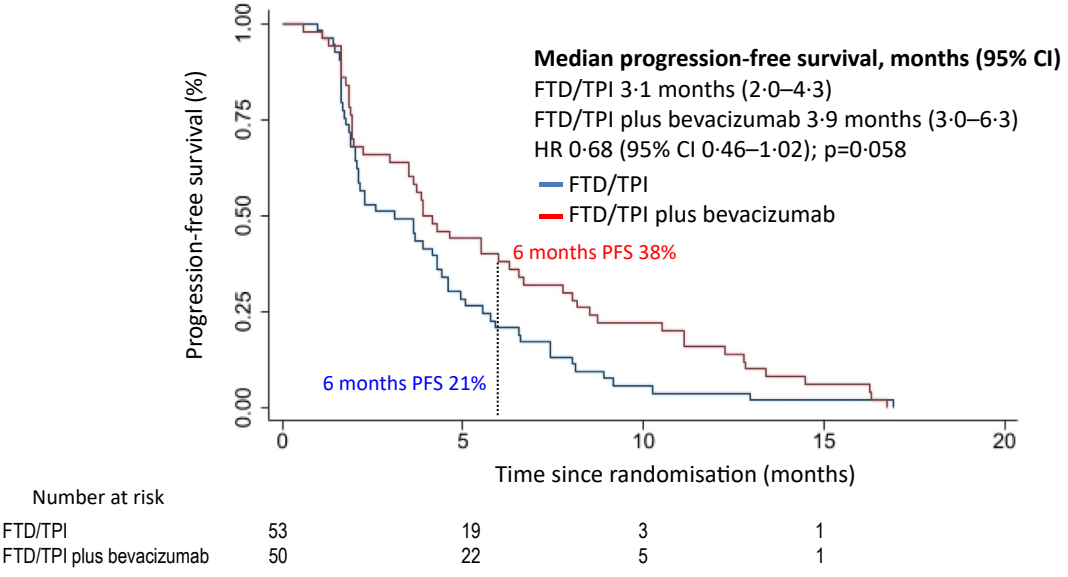

Fig. 2: Progression-free survival in months (95% CI). Abbreviation: PFS, progression-free survival; FTD/TPI, trifluridine-tipiracil.

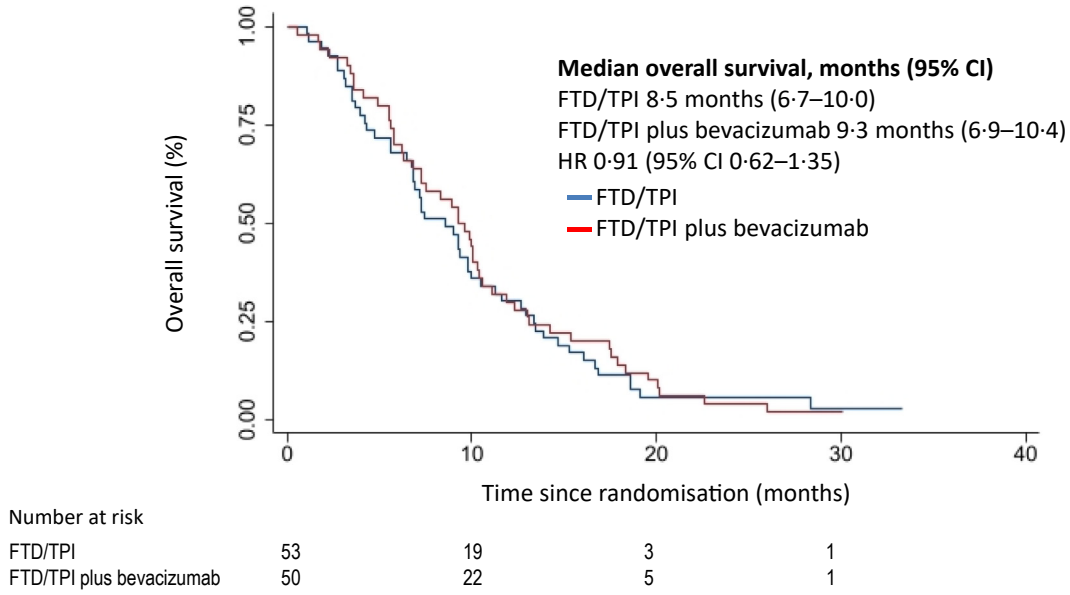

Fig. 3: Overall survival in months (95% CI). Abbreviation: OS, overall survival; FTD/TPI, trifluridine-tipiracil.

group (3.4 months vs 1.8 months), as well as the doubling in median number of treatment cycles (four vs two). The discontinuation percentages due to progression were similar in the monotherapy and combination arm, 85% vs 84% and reflect the final cause of stopping treatment without a time aspect. The percentage of patients with progressive disease as their best response, was numerically higher in the monotherapy arm (42%) than in the combination arm (32%) (Table 4), which could explain, why patients stayed longer on therapy in the combination arm. Also of note, the fraction of patients alive and without progression at six and twelve months were both numerically longer in the combination treatment. As expected, very few patients obtained an objective response, but there was a numerically higher DCR in the combination arm vs the standard arm (66% vs 53%). Two-third of the patients (35 patients in each arm) had a dose-delay, which could have introduced a bias, as progression of disease is almost always detected on CT, especially when PFS is short. It could partly explain, why the PFS difference is not reflected in an OS difference. In our trial, 54% of patients received the treatment as second-line, which increases the likelihood of receiving further lines of treatment. In a subset of patients all treated at one centre, 18 of 35 patients (51%) received subsequent

	Trifluridine/tipiracil monotherapy (n = 53)		Trifluridine/tipiracil plus bevacizumab (n = 50)	
	Any grade	Grade≥ 3	Any grade	Grade≥ 3
At least one hospitalisation		21 (40%)		22 (44%)
Haematological toxicity				
Neutrophil count decreased	41 (77%)	26 (49%)	39 (78%)	23 (46%)
Anaemia	46 (87%)	5 (9%)	41 (82%)	5 (10%)
Platelet count decreased	10 (19%)	1 (2%)	13 (26%)	1 (2%)
Non-haematological toxicity				
Nausea	34 (64%)	3 (6%)	30 (60%)	3 (6%)
Diarrhoea	17 (34%)	0 (0%)	20 (40%)	2 (4%)
Vomiting	16 (30%)	1 (2%)	21 (42%)	4 (8%)
Fatigue	44 (83%)	2 (4%)	45 (90%)	5 (10)
Febrile neutropenia		4 (8%)		5 (10%)

Data are n (%).

Table 3: **Adverse events in 103 patients receiving trifluridine/tipiracil monotherapy or trifluridine/tipiracil plus bevacizumab.**

Response	FTD/TPI monotherapy	FTD/TPI plus bevacizumab
Patients, n	53	50
Response rate	1 (2%) (95% CI 0%–10%)	4 (8%) (95% CI 2%–19%)
Complete response	0 (0%)	0 (%)
Partial response	1 (2%)	4 (8%)
Stable disease	27 (51%)	29 (58%)
Progressive disease	22 (42%)	16 (32%)
Non-evaluable	3 (6%)	1 (2%)

Note: all four non-evaluable patients had only baseline CT performed and were excluded from study due to patient wish, toxicity, bleeding from primary tumor and general poor condition.

Table 4: **Response rate.**

line(s) of therapy, also partly explaining the discrepancy between PFS and OS, as OS could be affected by post-progression therapies.

In our trial, the combination of FTD/TPI and bevacizumab was not associated with significantly increased toxicity.

This trial has several limitations. As PFS is calculated from the date of randomisation to the first date of radiological or clinical progression, time till death, or censored on cut-off date, it is not a completely objective endpoint, as the determination of clinical response is not objective. It could therefore have been influenced by the open-label design. In our trial, 8 patients (8%) were noted to have clinical progression of disease. Also, the lack of central assessment of imaging could introduce a bias in evaluation of the radiological response, and thereby affect assessment of the primary endpoint. Both factors influence the internal validity of the trial. The open-label design also risks the patients underreporting of adverse events.

Despite not reaching statistical significance in our trial, in our opinion the combination of FTD/TPI and anti-angiogenic therapy with bevacizumab warrants further investigation in a larger trial.

The Lon-Gas trial is the first randomised trial to compare trifluridine/tipiracil to trifluridine/tipiracil plus bevacizumab in patients with pre-treated esophagogastric cancer. The combination of trifluridine/tipiracil plus bevacizumab did not significantly prolong PFS and OS, but possible indications of efficacy on several, secondary parameters were seen, which merits further evaluation in a larger trial with OS as primary endpoint.

Contributors

LBJ, PP, CQ, MY, MN and ML comprised the steering committee and participated in all phases of the trial, including the design of the trial, writing of protocol and amendment, analyses, and interpretation of the data and preparation of the manuscript. LBJ, PP, CQ, MY, MN and ML recruited patients and gathered data for the trial. ICE, PP, and SM did the statistical analyses. All authors interpreted the data and were involved in the review and approval of the manuscript and the decision to submit for publication. All authors read and approved the final version of the manuscript.

Data sharing statement

The data collected for this trial can be made available to others in de-identified form after all primary and secondary endpoints have been published and in the presence of a data transfer agreement and if the purpose of use complies with Danish legislation. Requests for data sharing can be made to the corresponding author, including a proposal that must be approved by the trial's steering committee.

Declaration of interests

LBJ reports a research grant from the Danish Cancer Society. LBJ reports a research grant from medical company Servier, including coverage of FTD/TPI medical expenses. LBJ reports a research grant from medical company Roche, partly covering medical expenses for bevacizumab. All grants were transferred to and administered at a hospital research account, subject to public audit. There was no financial gain for the departments involved. None of the involved staff has any economic involvement in this trial. Patients received no economic compensation for participation in the trial. PP reports research funding from Servier, during the conduct of the trial. CQ reports travel grant from Servier, during the conduct of the trial. ML reports research funding from Scandion Oncology and research grant from Danish Cancer Society. ML participated on a Data Safety Monitoring Board at Scandion Oncology, Denmark. All other authors report no competing interests.

Acknowledgements

We thank the Good Clinical Practice units in Denmark for monitoring the trial. We thank the patients and their families and the trial investigators, nurses, and colleges.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102521.

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