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A phase 1b multicenter study of TAS-102 in combination with irinotecan in patients with advanced recurrent or unresectable gastric and gastroesophageal adenocarcinoma after at least one line of treatment with a fluoropyrimidine and platinum-containing regimen

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Abstract

TAS-102 is approved for treatment of refractory metastatic gastroesophageal carcinoma (mGEC). This study sought to determine whether the combination of TAS-102 with irinotecan (TASIRI) was safe and effective in previously treated mGEC. This was a single-arm phase 1b study for patients (pts) with mGEC previously treated with at least one line of fluoropyrimidine and platinum-containing regimen. TAS-102 was given at 25 mg/m^2 twice daily on days 1 to 5 with irinotecan 180 mg/m^2 on day 1 of a 14-day cycle. The primary endpoint was progression-free survival at 6 months ≥ 35% (PFS-6). 20 Pts were enrolled. The study met its primary endpoint. PFS-6 is 40% (95% CI 19.3–60.0). Median PFS and overall survival are 5.3 months and not reached, respectively. 17 of 20 pts had measurable disease by RECIST criteria. Of the 17, 13 had stable disease and 4 had progressive disease as best response (8 pts had tumor shrinkage < 30%). The disease control rate was 75%. In exploratory analyses, mutations in homologous recombination deficiency genes were associated with inferior PFS ($P < 0.03$). The most common any grade (G) treatment-related adverse events (TRAE) were nausea ($n = 14$, 70%), diarrhea ($n =$ 9,45%), and fatigue ($n = 8$, 40%). G3–4 TRAE in > 5% of pts were anemia (20%) and neutropenia (10%). 2 serious TRAE were reported: G4 febrile neutropenia ($n = 1$) and G3 hypotension ($n = 1$).

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Author contributions FD designed the study. KT, EK, SE, JV, and MTC collected the data. FD and THT analyzed the data. All authors wrote the manuscript.

Conflict of interest FD has received research grants (to the institution) from AstraZeneca, Bristol-Myers Squibb, Merck, Genentech/Roche, Taiho, Exelixis, Trishula, and Leap Therapeutics, has received a speaker honorarium from Amgen, Eisai, Ipsen, Exelixis, Sirtex, Deciphera, Ipsen, and Natera, and has received a consultancy honorarium from Natera, QED, Eisai, Exelixis, and Genentech/Roche. MTC has received research grant (to the institution) from Bristol-Myers Squibb, a speaker honorarium from Pfizer, Natera, Taiho, BMS, AstraZeneca, a consultancy honorarium from Amgen, Incyte, Eisai, Ipsen, Astellas, Taiho, Exelixis, QED, I-Mab, Tempus, Seattle Genetics, HelioDx, Bayer, AstraZeneca, Genentech/Roche, Pfizer, Natera, Taiho, BMS, and Basilea. EJK has received a consultancy honorarium from Taiho. The other authors declare that they have no conflict of interest.

There was no G5 TRAE. The combination of TASIRI showed encouraging clinical activity with a meaningful improvement in PFS-6 compared to historic controls.

Keywords

Gastric cancer; Chemotherapy; Survival

Introduction

Gastric cancer (GC) is the 5th leading cancer and the 3rd leading cause of cancer-related deaths worldwide [1]. In the United States and Europe, where screening is infrequent, 40% of newly diagnosed GC cases present as advanced disease. As opposed to 20% in Japan and Korea, where early detection is common [2]. Gastroesophageal junction cancer anatomically straddles the distal esophagus and proximal stomach. Due to its anatomic location and given that, like GC, the majority of GEJ tumors are adenocarcinomas, GEJ tumors are frequently grouped together with GC and are treated in a similar fashion to GC [3]. Platinum compounds (oxaliplatin and cisplatin) and fluoropyrimidines (5-fluorouracil or capecitabine) are generally considered as first-line (1L) for metastatic gastroesophageal carcinomas (mGEC) [4, 5]. More recently, the anti-PD1 monoclonal antibody nivolumab showed improved survival when added to the chemotherapy doublet, especially in patients (pts) with PD-L1-positive tumors [6].

About 50% of pts with mGEC progressing after 1L are eligible for subsequent lines of treatment [7]. In second-line (2L) plus mGEC, taxanes with or without ramucirumab, irinotecan, and pembrolizumab in select pts (PD-L1-positive in third-line (3L) plus or MSI-high in 2L plus) are recommended treatment options [8, 9]. Irinotecan has been tested in multiple single-arm and randomized trials in 2L plus mGEC, with reported ORR in the 15–29% range and median PFS of 2–3 months [10, 11]. The largest current randomized phase-3 trial in 2L mGEC was the RAINBOW trial, demonstrating an improvement in mOS, mPFS, and ORR with the combination of paclitaxel plus ramucirumab vs. paclitaxel alone [8]. Despite these advances, outcomes for advanced GEC remain poor with a mOS of 9.6 months and PFS-6 of only 36% [8].

Until recently, no randomized phase-3 trial demonstrated a survival benefit in 3L plus mGEC. TAS-102 is an orally available combination drug of an antineoplastic thymidine-based nucleoside analogue, 1 M trifluridine (FTD), and 0.5 M tipiracil hydrochloride (TPI). TPI inhibits degradation of FTD by thymidine phosphorylase (TP). Following uptake into cells through nucleoside transporters, FTD is converted to its monophosphate F3dTMP by thymidine kinase. After further phosphorylation steps, its triphosphate F3dTTP is incorporated into DNA as substitute for thymidine triphosphate [12]. The TAGS trial randomized 507 pts with 3L + mGEC in 2:1 ratio to either TAS-102 or placebo and showed a significant improvement in mOS from 3.6 to 5.7 months (HR 0.69, $P = 0.0003$) [13].

One of the clinical challenges of 2L treatment with taxanes after 1L platinum-containing regimens (in the US, mainly oxaliplatin) is the development and worsening of peripheral neuropathy, which often leads to dose reductions, treatment delays, and reduced quality

of life for pts. In the RAINBOW trial, 46% of pts in the combination arm developed neuropathy, 8% of which were G3. The WJOG 4007 trial compared irinotecan with paclitaxel in 2L mGEC and found no difference in survival [14]. Thus, irinotecan can be regarded as one possible current standard option for 2L + mGEC. Early-phase trials have evaluated the feasibility of TAS-102 in combination with irinotecan +/− bevacizumab in pts with advanced colorectal adenocarcinoma. Doi et al. completed a 3 + 3 dose escalation study and established a recommended dose of 50 mg/m^2/day (corresponding to 25 mg/m^2 bid) on days 1–5 and 8–12 with irinotecan 150 mg/m^2 on days 1 and 15 of a 28-day cycle [15]. More recently, TAS-102 was combined with irinotecan and bevacizumab in metastatic colorectal carcinomas (mCRC) in a modified dosing schedule (TAS-102 at 25 mg/m^2 bid daily on days 1 to 5, irinotecan 180 mg/m^2 day 1, bevacizumab 5 mg/kg day 1, given every 14 days). The authors did not report any new safety signals and encouraging activity in a cohort of heavily pretreated pts [16].

Based on the considerations above, we sought to determine the clinical activity of TAS-102 with irinotecan (TASIRI) in a real-world population of pts with mGEC with limited approved treatment options.

Materials and methods

Study design and patients

This was a single-arm, open-label phase 1b clinical trial performed at the University of California (Irvine and Davis sites). Pts had histologically or cytologically confirmed gastric or gastroesophageal adenocarcinoma, which was locally advanced, recurrent, or metastatic and not amenable to curative intent surgery. They had progressed, or not tolerated, at least one line of treatment with a platinum and/or fluoropyrimidine-containing regimen. 1L was defined as at least one cycle of combination chemotherapy including a platinum and/or fluoropyrimidine-based regimen for advanced disease. Pts with Her-2 overexpressed tumors had received prior trastuzumab. Combination regimens with platinum/fluoropyrimidine containing a taxane and or an immune checkpoint inhibitor (CPI) were allowed. Pts progressing within six months of perioperative chemotherapy or definitive chemoradiation for localized disease were eligible. Pts who had exhausted all other standard of care options were also eligible. Pts were ≥ 18 years old, with an ECOG performance status of 0–2, and a life expectancy greater than 3 months based on investigator's assessment. Pts who had major surgery within 4 weeks, or chemotherapy or radiotherapy within two weeks prior to entering the study, those with prior treatment with irinotecan or TAS-102, and those with known brain metastases were excluded. The trial was approved by the Institutional Review Board at the University of California Irvine (protocol number HS#2019-5179), and adhered to good clinical practice guidelines. All pts provided written, informed consent as a condition of study participation. The study was registered at ClinicalTrials.gov (NCT04074343).

Procedures

Pts were treated with TAS-102 25 mg/m^2 p.o. bid on days 1–5 and irinotecan 180 mg/m^2 i.v. on day 1 every 14 days. If the absolute neutrophil count (ANC) was less than 1500/μL on day 1 of a cycle, then treatment was delayed until ANC had recovered and g-csf 5 mcg/kg

was added on day 6 for 3 to 5 days. Ondansetron and diphenoxylate hydrochloride and atropine sulfate at standard doses were prescribed to manage associated nausea/vomiting and diarrhea/cramping at home. All pts who received treatment on this protocol were evaluable for toxicity. Toxicity was assessed prior to each cycle according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0 [17]. Predefined permanent dose adjustments were allowed based on occurrence of intolerable G2 or G3–4 adverse events. The first dose reduction was TAS-102 20 mg/m^2 p.o. bid on days 1–5 and irinotecan 144 mg/m^2 i.v. on day 1. If a second dose reduction was required, TAS-102 was discontinued and irinotecan reduced to 108 mg/m^2. Participants were treated on protocol until disease progression defined as radiographic progression by RECIST v1.1 criteria [18], death or symptomatic progression as clinically determined by the treating physician, unacceptable toxicity, or withdrawal of consent. Radiographic tumor assessments using computed tomography (CT) of the chest, abdomen and pelvis were performed at baseline and every 8 weeks thereafter for the duration of the study. Magnetic resonance imaging of the abdomen and pelvis was permitted instead of CT scan based on the investigator's discretion. Tumor markers CEA (carcinoembryonic antigen) and CA19-9 (carbohydrate antigen 19-9) were measured prior to each cycle in pts with elevated baseline values.

Outcomes

The primary endpoint was 6 months progression-free survival (PFS-6). The secondary endpoints were rates of drug-related G3–5 adverse events experienced within the first 8 weeks (2 cycles) of study treatment. Other secondary end-points were best objective response rate by RECIST v1.1 in pts with measurable disease, median progression-free (PFS), and overall survival (OS).

Exploratory genomic analysis

An exploratory review of the mutational landscape was performed in pts with available comprehensive genomic analysis (i.e., performed as part of routine clinical care). A comparison of the frequency of homologous recombination deficiency (HRD)-associated genes [19] was done using the Fisher's exact test.

Statistical analysis

Based on recently published phase-3 data for mGEC, PFS-6 in 2L with optimal treatment is estimated at about 35% [7]. In 3L setting, the largest most contemporary randomized phase-3 trial of TAS-102 vs. best supportive care (BSC) defined a PFS-6 of 15% with single-agent TAS-102 vs 6% with BSC. The hypothesis was that the combination of TAS-102 and irinotecan would improve PFS-6 compared to these recent historical controls. To estimate the efficacy, $n = 20$ pts were required. If at least $n = 7$ pts had not progressed by 6 months (i.e., observed PFS-6 ≥ 35%), then the observed PFS-6 of 35% would have a one-sided lower 95% CI of 17.5% [18]. This means the lower boundary for estimated efficacy is as good as or better than currently available options in 3L setting. Efficacy was signaled by at least 7 out of 20 being progression-free at 6 months. If none of the first 14 evaluable enrollees was progression-free at 6 months, futility would be declared. PFS and OS were estimated by Kaplan–Meier method.

Results

Patient characteristics

Between September 12, 2019, and January 8, 2021, 23 pts were screened. Three pts were not eligible, and thus 20 eligible pts started the study treatment (Fig. 1). Table 1 shows the pt and disease characteristics. Most pts were male (75%), median age was 61 years (range 24–78), 30% were Hispanic, 20% were Asian, and the remaining were Caucasian. Thirteen pts (65%) had de novo unresectable advanced disease. All pts had received at least one line of treatment with a fluoropyrimidine and platinum agent (median lines of prior treatment: 2). The rates of prior treatment with a taxane and anti-PD1 antibody were 50% and 45%, respectively. At the time of data cut-off (June 13th, 2021), two pts remain on treatment with a median duration of follow-up of 10.0 months (range 2.4–20.2). The main reason for treatment discontinuation was disease progression.

Efficacy

The study met its primary endpoint with a PFS-6 of 40% (95% CI 19.3–60.0). Median PFS (Fig. 2) and OS (Fig. 3) were 5.3 months (95% CI 2.1–7.6) and not reached (95% CI 6.5–not evaluable), respectively. In 17 pts with measurable disease, best objective response was stable disease in 13 of 17 (75.5%) and progressive disease in four of 17 (23.5%) pts. No pt had a partial response or better by RECIST v1.1 criteria. However, 8 of 17 (47%) pts had a median tumor reduction of – 14.9% (range – 3.7 to – 20.0, Fig. 4). In pts with tumor reduction, median time to nadir was 10 weeks (range 8–42). 2 of 3 pts with no measurable disease at baseline remained on treatment for more than 6 months and 1 pt progressed before the first on-treatment imaging. Hence, in all 20 pts, the rate of disease control was 15 of 20, i.e., 75%.

Exploratory mutational landscape

A post hoc review of pt charts showed that comprehensive genomic panel analysis using commercially available tissue or plasma-based platforms was available for $n = 17$ pts. The most commonly observed mutation was *TP53 (*$n = 13$, 75.5%). *CDH1* mutations were observed in $n = 2$ pts (11.8%). HRD-related somatic gene mutations (*ARID1A, ATM, BRCA2, CHEK2, and FANCA*) occurred in $n = 5$ (29.4%) pts. Interestingly, all HRD-related mutations occurred in pts who had a PFS below the median of the overall population (5 of 9 pts, 55.6%), while none of the pts with PFS above the median harbored a HRD gene mutation (0 of 8, $P < 0.03$).

Safety

Table 2 shows treatment-related adverse events (TRAE). All pts reported at least one TRAE, and two pts experienced a serious TRAE (febrile neutropenia and hypotension, each $n = 1$). The most common AEs were nausea, diarrhea, fatigue, and abdominal pain. G3 or higher TRAEs included anemia ($n = 4$, 20%), decreased neutrophil count ($n = 2$, 10%), followed by diarrhea, abdominal pain, and vomiting (each $n = 1$, 5%). There were no G5 TRAEs.

A total of 251 cycles were administered. Full-dose irinotecan (180 mg/m^2) was given for 212 cycles, while a total of 18 cycles were delivered at dose level – 1 (144 mg/m^2), and 21

cycles at dose level – 2 (108 mg/m^2). TAS-102 was delivered at full dose (35 mg/m^2 bid) for a total of 219 cycles, and for 16 cycles at dose level – 1 (20 mg/m^2 bid). One pt received a total of 16 cycles without TAS-102 due to neutropenia (i.e., dose level – 2 per protocol). Thus, the relative dose intensity for irinotecan was slightly higher for irinotecan (95.2%) than for TAS-102 (90.1%).

Discussion

Platinum/fluoropyrimidine combinations, with or without PD1 inhibitors, followed by taxane-based regimens are currently accepted standard treatments in first and second line for mGEC [20]. Both platinum compounds (oxaliplatin, cisplatin) and taxanes (paclitaxel, docetaxel) used in mGEC are associated with peripheral neuropathy which might limit treatment duration and benefit [21]. As an acceptable alternative, irinotecan-based regimens have been used and are included in guidelines [20, 22]. More recently, the German Phase 2 RAMIRIS trial compared FOLFIRI + ramucirumab with paclitaxel + ramucirumab in 2L mGEC and did not demonstrate significant differences in PFS or OS between the two treatment arms [23]. Importantly, docetaxel pretreated pts appeared to derive a pronounced benefit of treatment with the irinotecan-based combination.

TAS-102 is an oral combination drug consisting of FTD, which is a thymidine-based nucleoside analog, and TPI, which improves the bioavailability of FTD by inhibiting its catabolism by (TP) [24]. The compound has demonstrated clinical activity after progression on traditional fluoropyrimidines such as 5-FU and capecitabine [13, 25]. Treatment with TAS-102 improves OS and is approved for 3L + mGEC and mCRC, but has shown modest single activity with objective response rates less than 10%. Varghese et al. demonstrated the safety and clinical activity of TAS-102 combined with irinotecan (with or without bevacizumab) as salvage treatment in heavily pretreated mCRC [16]. We used this trial to determine the dose levels used in the current study [16]. While we did not perform a formal phase 1 dose finding study due to already available data, we chose a phase 1b design (rather than a larger phase 2) design which enabled us to obtain data on clinical efficacy and safety in a timely manner without extensive financial resources.

We show the combination of TASIRI is feasible and active in a real-life population of mGEC. To ensure a rapid accrual, we sought to aim for a large effect size (i.e., more than double of PFS-6 expected in historic controls). This assumption also allowed us to minimize the required sample size. In our opinion, limiting pts by too restrictive eligibility criteria, including allowing only pts with measurable disease, does not fully capture real-life pts who nevertheless need treatment. In fact, researchers at MD Anderson Cancer Center in Houston, TX, were able to conduct a trial in pts who did not fit the standard eligibility criteria for clinical trials. The authors showed accrual in these pts is feasible and they still might benefit from trial participation [26].

With these considerations in mind, we specifically chose PFS-6 as the primary endpoint of this study. This allowed us to maximize the number of eligible pts (since not based on objective response rate), minimize sample size (since we aimed for a relatively large effect size), and achieve the primary endpoint rapidly (i.e., within 6 months after the last pt

enrolled or at the time of progression of the last pt enrolled, whichever occurred earlier). We were able to efficiently accrue at two sites within 15 months. Given the geographic location (California) with a high proportion of pts with Asian and Hispanic ethnicity (50%), we had a relatively high proportion of pts with associated aggressive histology (poorly differentiated and or signet cell histology) [27].

Most available data for the use of irinotecan in mGEC, either as single agent or in the FOLFIRI regimen, are based on 2L usage [10, 11, 14, 28]. The reported median PFS ranges from 2.2 to 3.8 months, with a rather consistent median OS of 6.2 to 6.7 months. In addition, a disease control rate (DCR) of 53–64% has been reported in these studies. Response rates of up to 22.8% have been reported in 2L use of irinotecan containing regimens. Interestingly, response rates do not appear to the significantly differ between single-agent irinotecan vs. FOLFIRI [11], nor do they appear to predict for survival. TAS-102 was studies in a real 3L setting as single agent, and while both median PFS (2.0 months) and OS were improved compared to placebo, no objective responses were observed. Therefore, the survival benefit seen from TAS-102 was mainly based on an improved DCR. Thus, based on available prior data shown here, the observed benefit of later line systemic treatment of mGEC appears to mainly driven by disease control rather than inducing deep tumor responses, which are uncommon. With these considerations in mind, our data appear to show favorable clinical activity of the TASIRI regimen with a numerically higher median PFS of 5.3 months compared to historical controls, even those based on 2L studies, and our cohort included at least 60% 3L + pts. It is important to consider that even though 40% of our pts had only 1 line of prior treatment for metastatic disease, this included pts who received a triplet taxane containing regimen upfront or had received already adjuvant chemotherapy prior to 1L treatment for mGEC. We observed in this heavily pretreated population a DCR of 75%, which again compares favorably to previously reported DCR rates with irinotecan containing regimens. The lack of objective responses is likely because most pts had prior exposure to multiple different active agents for mGEC and hence while we observed a tumor shrinkage in 50% of pts with measurable disease, the extent of tumor reduction did not qualify as objective response based on RECIST criteria.

We did not add ramucirumab since paclitaxel with ramucirumab is standard for 2L therapy for pts treated with 1L platinum/fluoropyrimidine doublets [8], but there are no data to endorse the use of ramucirumab in 3L plus or in pts who had taxane-based first-line regimen. Klempner et al. presented a case series of 2L FOLFIRI plus ramucirumab in mGEC with favorable efficacy and safety compared to historical controls treated with paclitaxel and ramucirumab [29]. Extrapolating from Klempner et al. and Varghese et al., the addition of ramucirumab in pts who receive TASIRI in 2L might be considered, but the additional data are needed in mGEC. It should be noted that in the TRUSTY study for 2L mCRC, TAS-102 plus bevacizumab was not found to be non-inferior to fluoropyrimidine, irinotecan, and bevacizumab combinations [30], possibly providing additional support for the strategy of combining TAS-102 with irinotecan [31]. Sixty percent of our pts had received at least two lines of therapy (i.e., 3L plus setting). The remaining 40% had either received a triplet regimen in first line, or had neuropathy which would preclude a treatment with a taxane, and hence would have been eligible for a 3L trial.

Based on multiple positive phase-3 trials [6, 32-34], CPIs are being used in combination with chemotherapy in 1L mGEC for PD-L1-positive tumors and were previously approved as single agent in 2L plus MSI-high solid tumors including mGEC [35] or 3L plus PD-L1-positive mGEC [36]. None of our pts were found to have MSI-high tumors. Although at the time of enrollment the results of none of the 1L mGEC CPI combination trials were available, 45% of our pts had been pretreated with CPI during a previous line of treatment. Despite the earlier use of CPI, at least in PD-L1 positive tumors, possibly even in the adjuvant setting [37, 38], there is still an unmet need for cytotoxic regimens for pts who do not respond or are not eligible for CPI.

Comprehensive genomic analysis of tumors (either by commercially available tissue or liquid-based platforms, or at some institutions using in house validated testing) has become more prevalent in routine clinical care, especially for pts with advanced malignancies [39]. Consistent with this notion, somatic mutational analysis was available for the majority (17 of 20) of pts in our study. While not pre-specified and somewhat limited due to retrospective nature of the analysis and relatively small sample size, we made some notable observations. Firstly, *TP53* mutations were by far the most frequent detected mutations in our pt cohort. Additionally, 5 of 17 pts had a HRD-related mutation, and all of those pts had a PFS below the median ($P < 0.03$). The favorable response of HRD-deficient tumors (especially germline mutated) to platinum compounds and PARP inhibitors is well documented [40]. However, the data for HRD mutations as predictive or prognostic factors beyond these compounds are more inconclusive [41-43]. Thus, at this time, it is not clear whether the observed shorter PFS in pts with HRD mutations is due to an intrinsic resistance to the study regimen, or indicative of a poorer prognostic group of pts. These findings would have to be prospectively validated in a future follow-up study.

In summary, TASIRI appears to be a feasible treatment option for pts with mGEC who have progressed on 2L of standard treatment or who are not eligible for 2L taxane-based treatment due to significant neuropathy. A larger comparative clinical trial is being designed to further elucidate the role of TASIRI for pts with mGEC.

Conclusions

In pts with pretreated advanced gastroesophageal adenocarcinomas, the combination of TAS-102 and irinotecan was safe and demonstrated encouraging clinical activity with an observed PFS-6 of 40%.

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Abbreviations

mGEC	Metastatic gastroesophageal carcinoma
GC	Gastric cancer
PFS-6	Progression-free survival at 6 months

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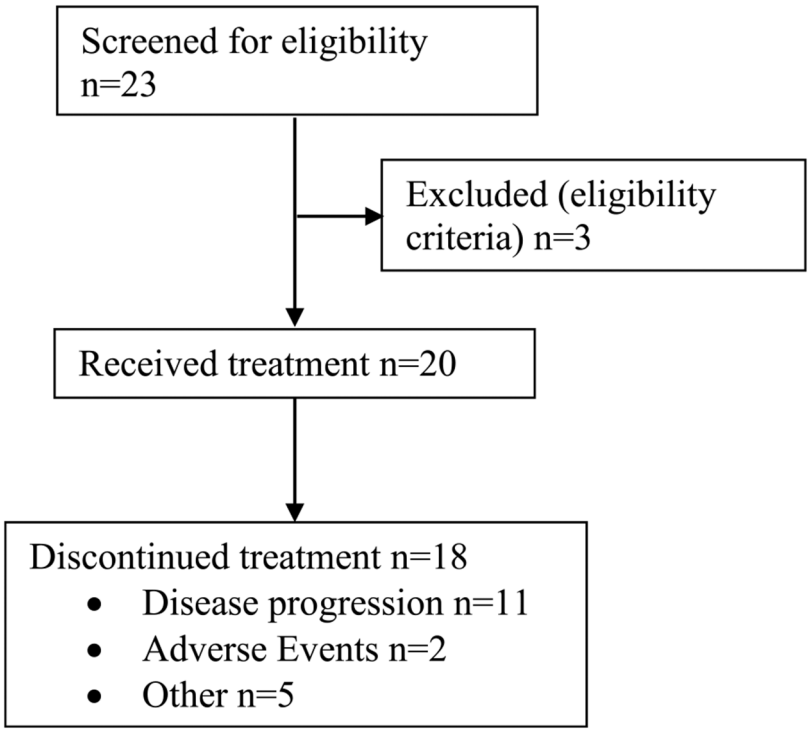

Fig. 1.
Trial enrollment

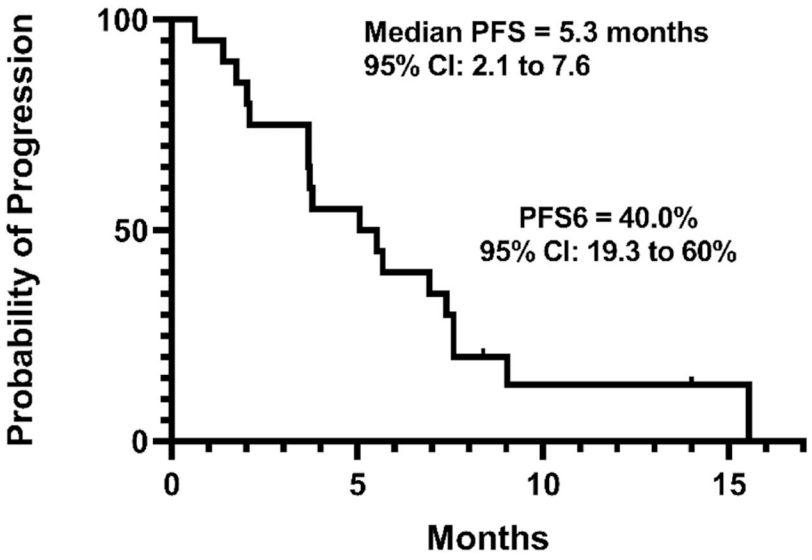

Fig. 2.
Progression-free survival

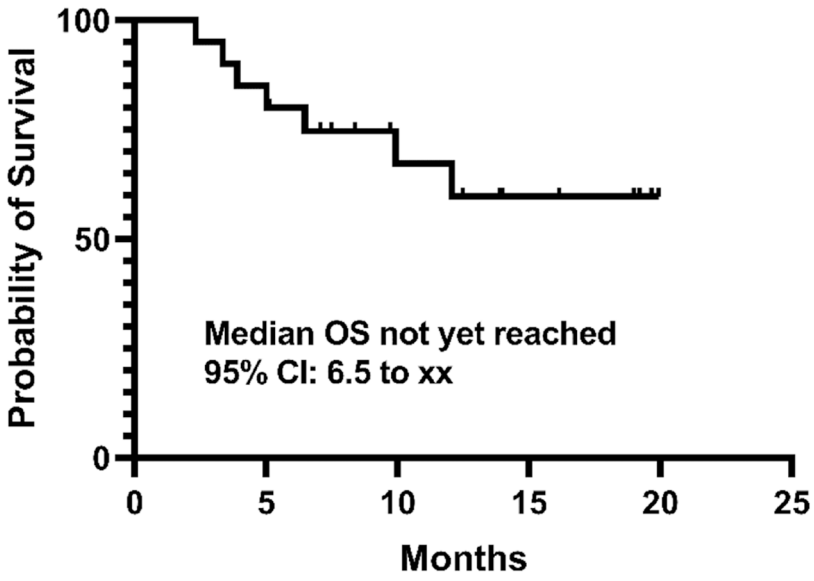

Fig. 3.
Overall survival

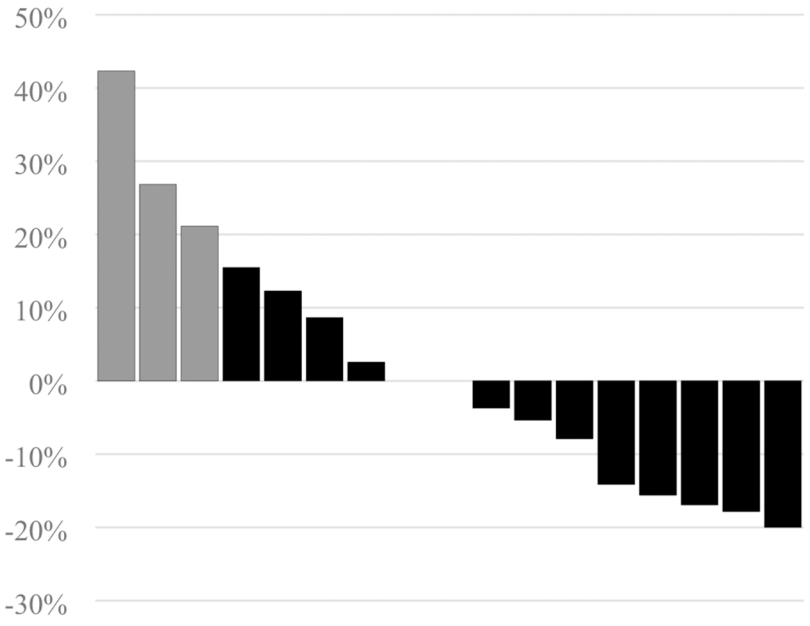

Fig. 4.

Waterfall plot. Percent change in target lesions compared to baseline in 17 patients with measurable disease. Gray bars: progressive disease; black bars: stable disease (by RECIST v1.1)

Table 1

Patient baseline characteristics

Total patients, *n* (%)	**20 (100)**
Age (years)	
Median	61
Range	24–78
Gender, *n* (%)	
Male	15 (75)
Female	5 (25)
Ethnicity, *n* (%)	
Caucasian	10 (50)
Hispanic	6 (30)
Asian	4 (20)
ECOG performance status, *n* (%)	
0	8 (40)
1	12 (60)
Tumor location, *n* (%)	
Gastroesophageal junction	10 (50)
Stomach	10 (50)
Stage at diagnosis, *n* (%)	
Stage I–III	7 (35)
Stage IV	13 (65)
Histologic grade, *n* (%)	
Grade 2	7 (35)
Grade 3	13 (65)
Signet cell present, *n* (%)	
Yes	5 (25)
No	15 (75)
Her-2 overexpression, *n* (%)	
Positive	5 (25)
Negative	15 (75)
Mismatch repair, *n* (%)	
Proficient	20 (100)
PD-L1 CPS score, *n* (%)	
≥ 1%	18 (90)
0%	2 (10)
Number of prior systemic treatments, *n* (%)	
1	8 (40)
2	8 (40)
≥ 3	4 (20)
Type of prior systemic treatments, *n* (%)	
Fluoropyrimidine	20 (100)

Total patients, *n* (%)	**20 (100)**
Platinum	20 (100)
Taxane	10 (50)
Checkpoint inhibitor	9 (45)
Other	10 (50)

Table 2

Treatment-related adverse events (≥ 5% frequency)

	Any grade	Grade ≥ 3
Any event, *n* (%)	20 (100)	8 (40)
Any serious event, *n* (%)	2 (10)	2 (10)
Most common events, *n* (%)		
Nausea	14 (70)	0 (0)
Diarrhea	10 (50)	1 (5)
Fatigue	10 (50)	0 (0)
Abdominal pain	7 (35)	1 (5)
Vomiting	6 (30)	1 (5)
Anorexia	6 (30)	0 (0)
Alopecia	4 (20)	0 (0)
Constipation	3 (15)	0 (0)
Headache	3 (15)	0 (0)
Mucositis oral	2 (10)	0 (0)
Hypotension	2 (10)	0 (0)
Laboratory abnormalities		
Neutrophil count decreased	6 (30)	2 (10)
Anemia	5 (25)	4 (20)
Hypokalemia	2 (10)	0 (0)
White blood cell decreased	2 (10)	0 (0)