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Original Research

A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201)☆

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KEYWORDS
TAS-102;
Gastric cancer;
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Phase II clinical trial;
Efficacy;
Safety;
Pharmacokinetic parameters

Abstract ***Aim:*** American phase I studies have reported that the recommended dose of TAS-102 (trifluridine/tipiracil) was 25 mg/m^2 twice a day (b.i.d.), although this schedule did not provide clinically relevant improvements in a phase II study of advanced gastric cancer (AGC). However, a pivotal phase III study revealed that TAS-102 at 35 mg/m^2 b.i.d. provided a clinically relevant improvement in overall survival (OS) among patients with metastatic colorectal cancer. Therefore, we re-evaluated the efficacy, safety, and pharmacokinetic parameters of TAS-102 at 35 mg/m^2 b.i.d among Japanese patients with AGC.
Methods: All patients had undergone one or two previous chemotherapy regimens that contained fluoropyrimidine, platinum agents, and taxanes or irinotecan. The primary end-point target was a disease control rate (DCR) of $\geq$50% after 8 weeks of the 35 mg/m^2 b.i.d. schedule.
Results: Twenty-nine patients were assessable after completing the 35 mg/m^2 b.i.d. schedule. The investigator-determined DCR was 65.5% (95% confidence interval [CI], 45.7–82.1%) and the independent central review's DCR was 51.9% (95% CI, 31.9–71.3%); both results exceeded the primary end-point target. The median progression-free survival and OS were 2.9 months (95% CI, 1.1–5.3 months) and 8.7 months (95% CI, 5.7–14.9 months), respectively. The grade III/IV adverse events included neutropenia (69.0%), leucopaenia (41.4%), anaemia (20.7%), and anorexia (10.3%). No AGC-specific toxicities were detected.
Conclusions: The 35 mg/m^2 b.i.d. dose of TAS-102 provided positive efficacy and an acceptable toxicity profile in patients with AGC. A randomised, double-blind, placebo-controlled, phase III study is ongoing to validate these findings.
Clinical trial registration number: UMIN000007421

1. Introduction

Gastric cancer is the third leading cause of cancer mortality, with 723,000 estimated deaths each year [1]. Fluoropyrimidine and platinum-based chemotherapies, with or without trastuzumab, are considered the global standards for first-line chemotherapy in patients with unresectable and recurrent gastric cancer [2,3]. Furthermore, taxanes, irinotecan, and ramucirumab (a novel vascular endothelial growth factor receptor-2 antibody) have recently emerged as standard second-line chemotherapy options [4–6]. However, the prognosis of patients with advanced or recurrent gastric cancer remains poor, with a median overall survival (OS) of 12 months.

TAS-102 (Taiho Pharmaceutical, Tokyo, Japan) is a novel oral nucleoside antitumour agent that comprised trifluridine (FTD) and tipiracil hydrochloride (TPI) at a molar ratio of 1:0.5 [7]. Five independent American phase I studies have defined the recommended dose schedule for TAS-102 as a 28-day cycle, with treatment on days 1–5 and 8–12 [8,9], and the maximum tolerated dosage was defined as 25 mg/m^2 twice a day (b.i.d.) in patients with intensively pre-treated breast cancer. However, an American phase II study of 25 mg/m^2 b.i.d. in patients with advanced gastric cancer (AGC) revealed only 1 case (5.6%) of stable disease (SD) among 18 patients and that study was closed after the first stage [10]. A phase I study was subsequently conducted in Japan, which evaluated a dosage of 35 mg/m^2 b.i.d., using the 28-day cycle from the American studies. This Japanese study reported grade IV neutropenia as a dose-limiting toxicity (DLT) in the 35 mg/m^2 b.i.d. schedule, and a higher dosage (40 mg/m^2 b.i.d.) was considered intolerable [11]. Therefore, a Japanese randomised phase II study and the international randomised phase III RECOURSE (Randomized, Double-Blind, Phase 3 Study of TAS-102 plus Best Supportive Care [BSC] versus Placebo plus BSC in Patients with Metastatic Colorectal Cancer Refractory to Standard Chemotherapies) study evaluated the 35 mg/m^2 b.i.d. dosage and reported clinically relevant improvements in OS and progression-free survival (PFS), compared to the placebo, among patients with metastatic colorectal cancer [12,13]. The results of the phase III study supported the approval of TAS-102 by the US Food and Drug Administration.

Because two patients with AGC did not exhibit severe toxicities at the 35 mg/m^2 dosage in the Japanese phase I study [11], we hypothesised that the 35 mg/m^2 b.i.d. dosage of TAS-102 would be feasible in patients with AGC. Therefore, we planned this open-label, single-arm, multicenter phase II study to evaluate the efficacy, safety, and pharmacokinetic (PK) profiles of TAS-102 monotherapy in patients with AGC.

2. Methods

2.1. Patient eligibility

This phase II study was conducted at six Japanese institutions and complied with the Declaration of Helsinki and the Good Clinical Practice guidelines. The study's protocol was independently prepared by the

investigators, was approved by the review boards of the participating institutions, and is listed in the UMIN registry (UMIN000007421). Written informed consent was obtained from all patients.

The key inclusion criteria were age of ≥20 years; unresectable or recurrent gastric or oesophagogastric junction adenocarcinoma; a history of one or two standard regimens that contained fluoropyrimidine, platinum derivatives, and taxanes or irinotecan; and documented progressive disease (PD) based on imaging data that were obtained during or within 2 months after the last treatment. The patients also had one or more measurable lesions, based on the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1), an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and adequate organ function.

2.2. Study treatment and assessment

A 35 mg/m^2 dose of TAS-102 was taken orally twice per day after meals, during a 28-d schedule with treatment on days 1–5 and 8–12. We also planned to evaluate the safety and PK parameters from six patients who were treated using a 40 mg/m^2 b.i.d. dosage in the same cycle. Treatment continued until tumour progression, unacceptable side-effects, or withdrawal of consent. Antitumour response was evaluated by each investigator at 4 and 8 weeks after treatment initiation, and then every 4–6 weeks, according to the RECIST guidelines. When treatment was discontinued for any reason, except for PD, follow-up imaging was performed according to the planned schedule until disease progression or subsequent anticancer treatment.

The primary end-point was the investigator-assessed disease control rate (DCR) for the 35 mg/m^2 b.i.d. dosage, which was defined as the proportion of patients with a best overall response of complete response (CR), partial response (PR), or SD, based on the RECIST guidelines. DCR was analysed in the per-protocol set over 8 weeks (PPS8W), which was the subset of patients who fulfilled the minimum exposure requirement (relative dose of ≥0.5) until 8 weeks or who experienced progression before the minimum exposure requirement without any major protocol deviation. Tumour response was confirmed after an independent review by a single radiologist (HK), who has 9 years of subspecialty experience in diagnostic oncologic radiology.

The secondary end-points were the objective response rate, PFS, OS, safety profile, and PK profile for the 35 mg/m^2 b.i.d. dosage. The safety and PK profiles of the 40 mg/m^2 b.i.d. dosage were also assessed. Furthermore, the dose intensity (DI) and relative DI (RDI) of the 35 and 40 mg/m^2 b.i.d. dosages were measured.

Safety analysis was performed in the safety population (SP), which comprised patients who received ≥1 dose of TAS-102. Adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0).

2.3. Statistical considerations

In the 35 mg/m^2 b.i.d. group, we considered a DCR of <30% to be unacceptable. Thus, based on Simon's Minimax two-stage design, we required 28 PPS8W patients to evaluate a null hypothesis (a DCR of ≤30%) with a one-sided $\alpha = 0.10$ and power of 80% to detect a clinically meaningful DCR (≥50%). In the first stage, 12 PPS8W patients were to be enrolled, and termination of the trial would be considered if three patients or less achieved DCR. The null hypothesis would be rejected if ≥12 patients experienced disease control. After completing the first stage, 17 additional patients (total 29 patients) were recruited for the second stage. This moderate increase in sample size resulted in $\alpha = 0.12$ and 84% power if the same threshold ($N = 12$) for disease control was used. We considered this modification as acceptable and applied the pre-planned threshold.

The objective response rate and DCR were calculated with their exact 95% confidence intervals (CIs). The Kaplan–Meier method was used to analyse PFS and OS, with estimates for median time-to-event end-points and the respective 95% CIs. All statistical analyses were performed using SAS software (release 9.3; SAS Institute Inc., Cary, NC, USA).

2.4. PK analysis

The PK parameters for the 35 and 40 mg/m^2 b.i.d. dosages, and the influence of gastrectomy, were investigated. Blood samples for the PK analyses were collected from six patients in the first stage of the 35 mg/m^2 b.i.d. dosage, in the following schedule: before administration and at 30 min and 1, 2 and 4 h after administration on days 1 and 12 of the first cycle. In the 40 mg/m^2 b.i.d. group, blood samples were collected from six patients in the following schedule: before administration and at 15 and 30 min and 1, 2, 4, 6, 8, and 10 h after administration on days 1 and 12 of the first cycle. The PK parameters for plasma FTD and TPI were calculated via non-compartmental methods using Phoenix® WinNonlin® software (Pharsight Corporation, St. Louis, MO, USA). The maximum plasma concentrations (C_{max}) and times to the maximum plasma concentration (T_{max}) were determined using the highest concentration and the time when it was observed. The area under the concentration–time curve (AUC) was calculated using the linear trapezoidal method on days 1 and 12. The comparisons of PK parameters in patients with solid tumours [11] or gastric cancer with/without gastrectomy were performed using Student t-test (C_{max} and AUC) and the Wilcoxon signed-rank test (T_{max}).

3. Results

3.1. Patient disposition

During the first stage, 12 PPS8W patients were enrolled in the 35 mg/m^2 b.i.d. group. Radiological evaluations revealed that eight patients achieved disease control. Therefore, we enrolled 17 patients for the second stage. All 29 enrolled patients were assessable as both SP and PPS8W. In the 40 mg/m^2 b.i.d. group, all six enrolled patients were assessable as both SP and PPS8W.

3.2. Patient characteristics

In the 35 mg/m^2 b.i.d. group (19 men [65.5%]; median age: 64 years [range: 35–76 years]), all patients had an ECOG PS of 0–1 (PS 0: 69%; PS 1: 31%) and had previously been treated using chemotherapy until disease progression. All patients had received fluoropyrimidine and platinum agents, while 18 patients (62.1%) had received taxanes and 11 patients (37.9%) had received irinotecan. Sixteen patients had previously undergone gastrectomy (55.2%). The characteristics of the six patients in the 40 mg/m^2 b.i.d. group were similar to those of the 35 mg/m^2 b.i.d. group (Table 1).

3.3. Exposure to chemotherapy

The 35 mg/m^2 b.i.d. group underwent a median treatment of three cycles (range: one to seven cycles), seven patients (24.1%) required a dose reduction, and nine patients (31.0%) interrupted their treatment. The RDI of TAS-102 was maintained in all treatment periods (median: 80.0%, range: 55.0–100%), and most patients (82.8%) were treated until disease progression. There was no marked difference in RDI between the patients with and without gastrectomy. The RDI of the 40 mg/m^2 b.i.d. group was maintained (median 98.3%, range 83.8–100%), and all six patients were treated until disease progression (Supplementary Table 1).

3.4. Efficacy

The best overall responses for the 35 mg/m^2 b.i.d. group were evaluated by the investigators and an independent radiological review (Table 2). The investigators' assessments of the PPS8W population revealed that 1 patient achieved PR and 18 patients achieved SD, which corresponded to an investigator-assessed DCR of 65.5% (95% CI, 45.7–82.1%). Nineteen patients achieved disease control, which exceeded the threshold of 12 patients, and the lower limit of the 80% CI value (51.9%) exceeded the predetermined threshold of 30% ($p < 0.0001$). Although none of the patients achieved CR, a decrease in the tumour size was observed in 41.4% of the patients (Fig. 1). The patients who exhibited a decrease in tumour size also exhibited a trend towards prolonged PFS (Fig. 1). In the exploratory analyses of the 40 mg/m^2 b.i.d. group, we observed three cases of SD and three cases of PD (DCR, 50%).

During the independent central review of the 35 mg/m^2 b.i.d. group, the radiologist concluded that two patients had no measurable tumour lesions based on the RECIST guidelines and that three patients who were

Table 1
Patient characteristics.

		35 mg/m^2 b.i.d. (N = 29)	40 mg/m^2 b.i.d. (N = 6)
		N (%)	N (%)
Age, years	Median (range)	64 (35–76)	58 (34–74)
Sex	Male	19 (65.5)	5 (83.3)
	Female	10 (34.5)	1 (16.7)
Performance status	0	20 (69.0)	4 (66.7)
	1	9 (31.0)	2 (33.3)
Previous gastrectomy	Yes	16 (55.2)	2 (33.3)
	No	13 (44.8)	4 (66.7)
No. of prior regimens	1	5 (17.2)	1 (16.7)
	2	24 (82.8)	5 (83.3)
Reason for discontinuing previous treatment	Disease progression	29 (100)	6 (100)
	Adverse event	0 (0)	0 (0)
	Other	0 (0)	0 (0)
Prior chemotherapeutic agents	Fluoropyrimidine	29 (100)	6 (100)
	Platinum agents	29 (100)	6 (100)
	Taxanes	18 (62.1)	3 (50.0)
	Irinotecan	11 (37.9)	3 (50.0)
Site of metastasis	Lymph nodes	20 (69.0)	4 (66.7)
	Liver	9 (31.0)	1 (16.7)
	Peritoneum	10 (34.5)	1 (16.7)
	Lungs	5 (17.2)	0 (0)
	Other	10 (34.5)	2 (33.3)

b.i.d., twice a day.

Table 2
Efficacy in patients (PPS8W) who were treated using the 35 mg/m^2 b.i.d. dose.

	By the investigators (N = 29)	Central review (N = 27)[b]
CR (N, %)	0 (0)	0 (0)
PR (N, %)	1 (3.4)[a]	1 (3.7)[a]
SD (N, %)	18 (62.1)	13 (48.1)
PD (N, %)	10 (34.5)	13 (48.1)
DCR (%); 95% CI	65.5; 45.7–82.1	51.9; 31.9–71.3
RR (%); 95% CI	3.4; 0.1–17.8	3.7; 0.0–19.0
Median PFS (months); 95% CI	2.9; 1.1–5.3	
Median OS (months); 95% CI	8.7; 5.7–14.9	

b.i.d., twice a day; PPS8W, the per-protocol set over 8 weeks population; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DCR, disease control rate; CI, confidence interval; RR, response rate; PFS, progression-free survival; OS, overall survival.

[a] The PR was not confirmed because the patient had to discontinue the study treatment due to prolonged liver dysfunction.

[b] The central radiologist judged that two patients had no measurable tumour lesions.

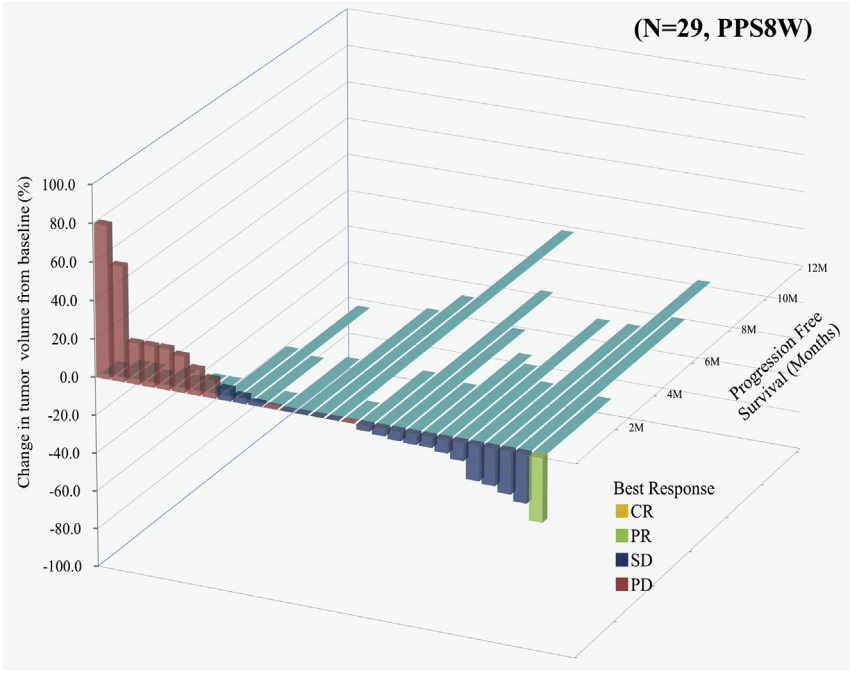

Fig. 1. Waterfall plot analysis for the 35 mg/m^2 twice a day cohort. One patient achieved partial response and the remaining 18 patients exhibited stable disease. The disease control rate according to the investigators was 65.5% (95% confidence interval, 45.7–82.1%). A decrease in the tumour size, compared to baseline, was observed in 41.4% of the patients and the patients who exhibited a decrease in tumour size also exhibited a trend towards longer progression-free survival. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

thought to exhibit SD actually had PD. Therefore, the DCR according to the independent central review was 51.9% (95% CI, 31.9–71.3%) (Table 2). However, the number of patients who achieved disease control (n = 14) still exceeded the predetermined threshold of 12 patients.

At the data cut-off point, all patients in the 35 mg/m^2 b.i.d. group had experienced disease progression and 20 patients had died. The median investigator-assessed PFS was 2.9 months (95% CI, 1.1–5.3 months) (Fig. 2, Table 2), and 36.4% (95% CI, 19.4–53.7%) of the patients were free from progression at 4 months. After a median follow-up of 17.1 months, the median OS was 8.7 months (95% CI, 5.7–14.9 months) (Fig. 2, Table 2).

3.5. Safety

The common grade III/IV AEs in the 35 mg/m^2 b.i.d. group were neutropenia (69.0%), leucopaenia (41.4%), anaemia (20.7%), and anorexia (10.3%) (Table 3). Serious AEs were reported for eight patients, although seven of these eight patients did not exhibit a confirmed causal relationship between TAS-102 treatment and the AEs. One case of febrile neutropenia occurred, although no treatment-related deaths were reported. Most patients (96.5%) underwent treatment as outpatients. Only one patient experienced a >10% reduction in body weight during the treatment. Although grade III/IV neutropenia (83.3%) and leucopaenia (66.7%) were slightly more frequent in the 40 mg/m^2 b.i.d. group, we did not observe any significant differences in the toxicity profiles for the 35 and 40 mg/m^2 b.i.d. dosages (Table 3).

3.6. PK analysis

When we compared the PK parameters for FTD and TPI between the 35 and 40 mg/m^2 b.i.d. dosages, the average C_{max} and AUC values for FTD and TPI exhibited dose-dependent increases (Table 4). There were no significant differences in the C_{max}, AUC, and T_{max} values for FTD and TPI at the 35 mg/m^2 b.i.d. dosage when we compared the patients with and without gastrectomy (Supplementary Table 2).

4. Discussion

The 35 mg/m^2 b.i.d. dosage schedule for TAS-102 monotherapy provided an investigator-assessed DCR of 65.5%. Furthermore, the independent review's DCR was 51.9%. Despite this adjustment, the number of patients who achieved disease control exceeded the threshold of 12 patients in both analyses. Moreover, 41.4% of the patients experienced a decrease in tumour size, with a median PFS of 2.9 months and a median OS of 8.7 months. Therefore, we conclude that the 35 mg/m^2 b.i.d. dosage of TAS-102 provided clinically relevant

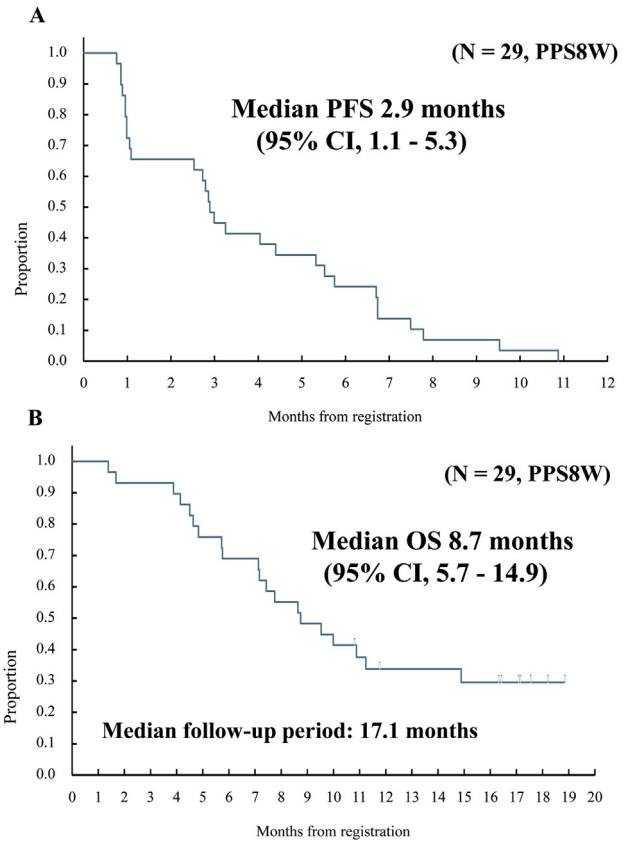

Fig. 2. Kaplan–Meier plots of PFS and OS in the 35 mg/m^2 twice a day cohort. At the data cut-off point (15th January 2014), all patients had experienced disease progression. (A) The investigator-determined median PFS was 2.9 months (95% confidence interval [CI], 1.1–5.3) and 36.4% (19.4–53.7) of the patients were progression free at 4 months. (B) At the data cut-off point, 20 patients had died. Based on a median follow-up time of 17.1 months, the median OS was 8.7 months (95% CI, 5.7–14.9). OS, overall survival; PFS, progression-free survival; PPS8W, the per-protocol set over 8 weeks population.

A recent international phase III study reported that ramucirumab provided significant improvements in PFS and OS, compared to a placebo, in patients with AGC who failed first-line platinum- or fluoropyrimidine-containing chemotherapy (median PFS: 2.1 months; median OS: 5.2 months) [6]. Interestingly, the present single-arm phase II study of TAS-102 monotherapy revealed favourable median PFS and OS values in patients with AGC, compared to those in the ramucirumab study. Furthermore, the present study examined the toxicity profile of TAS-102, which was comparable to those from phase II and phase III studies of patients with colorectal cancer. Moreover, we did not observe any disease-specific toxicities or complications in the present study, and the PK analyses revealed FTD concentrations that were similar to those in patients with solid tumours from the Japanese phase I trial [11]. Finally, we did not observe any significant differences in the PK parameters when we compared patients with and without gastrectomy.

In the Japanese phase I trial of TAS-102, the 35 mg/m^2 b.i.d. dosage was recommended by the Data and Safety Monitoring Board because they expected higher frequencies of grade IV neutropenia and DLTs at the higher dose, despite the maximum tolerated dose not being reached [11]. In the present trial, we evaluated the toxicity and PK profiles of the 40 mg/m^2 b.i.d. dosage and observed a dose-dependent increase in the concentration of FTD (versus that from the 35 mg/m^2 b.i.d. dosage). In contrast, there were no significant differences in these two dosages' toxicity profiles, although grade III/IV neutropenia and leucopaenia were slightly more frequent at the 40 mg/m^2 b.i.d. dosage. Nevertheless, the DCR at the 40 mg/m^2 b.i.d. dosage was 50.0% (SD: three patients; PD: three patients), and no patients achieved PR. Therefore, these results suggest that the 35 mg/m^2 b.i.d. dosage of TAS-102 provides positive clinical, toxicity, and PK-related outcomes in patients with AGC.

Table 3
Major adverse events.

	35 mg/m^2 b.i.d. (N = 29)		40 mg/m^2 b.i.d. (N = 6)	
	Any grade N (%)	Grade III/IV N (%)	Any grade N (%)	Grade III/IV N (%)
Haematological				
Neutropenia	25 (86.2)	20 (69.0)	6 (100)	5 (83.3)
Febrile neutropenia	1 (3.4)	1 (3.4)	0 (0)	0 (0)
Leucopaenia	26 (89.7)	12 (41.4)	6 (100)	4 (66.7)
Anaemia	25 (86.2)	6 (20.7)	5 (83.3)	1 (16.7)
Non-haematological				
Anorexia	24 (82.8)	3 (10.3)	4 (66.7)	1 (16.7)
Nausea	19 (65.5)	1 (3.4)	4 (66.7)	1 (16.7)
Vomiting	8 (27.6)	1 (3.4)	2 (33.3)	1 (16.7)
Diarrhoea	10 (34.5)	0 (0)	2 (33.3)	0 (0)
Abdominal pain	5 (17.2)	0 (0)	0 (0)	0 (0)
Constipation	5 (17.2)	0 (0)	2 (33.3)	0 (0)

b.i.d., twice a day.

benefits (comparable to those from studies of metastatic colorectal cancer) in patients with AGC who had been treated using fluoropyrimidine, platinum, and taxanes or irinotecan.

In conclusion, the 35 mg/m^2 b.i.d. dosage of TAS-102 monotherapy may be a useful treatment option

Table 4
Pharmacokinetic parameters of trifluridine and tipiracil hydrochloride in patients with gastric cancer.

	Solid tumour[a]		Gastric cancer			
	35 mg/m^2 b.i.d. (N = 6)		35 mg/m^2 b.i.d. (N = 6)		40 mg/m^2 b.i.d. (N = 6)	
	Day 1	Day 12	Day 1	Day 12	Day 1	Day 12
FTD						
C_{max} (ng/ml)	3338 ± 767	4752 ± 1697	4540 ± 1340	6560 ± 1200	3990 ± 1340	5870 ± 1780
T_{max} (h)	1.3 ± 0.5	1.9 ± 1.6	1.0 ± 0.5	1.5 ± 0.5	2.0 ± 1.1	2.2 ± 1.0
AUC_{0-10} (ng·h/ml)	8678 ± 1786[b]	20,950 ± 2237	7670 ± 1580[c]	18,100 ± 5770[c]	12,000 ± 3900	31,300 ± 10,300
AUC_{inf} (ng·h/ml)	8672 ± 1710	–	–	–	12,300 ± 4200	35,100 ± 12,100
$t_{1/2}$ (h)	1.41 ± 0.38	1.97 ± 0.51	–	–	1.58 ± 0.39	2.50 ± 0.49
TPI						
C_{max} (ng/ml)	76.6 ± 32.1	70.0 ± 43.4	85.6 ± 29.7	100 ± 41	89.5 ± 48.2	98.1 ± 36.9
T_{max} (h)	2.3 ± 0.8	2.3 ± 0.8	2.0 ± 0.0	1.8 ± 0.4	3.3 ± 1.0	3.3 ± 1.6
AUC_{0-10} (ng·h/ml)	281 ± 99[b]	317 ± 182	231 ± 79[c]	303 ± 149[c]	422 ± 170	466 ± 159
AUC_{inf} (ng·h/ml)	302 ± 96	–	–	–	446 ± 178	521 ± 185
$t_{1/2}$ (h)	1.67 ± 0.22	2.37 ± 0.93	–	–	1.67 ± 0.11	2.02 ± 0.40

b.i.d., twice a day; FTD, trifluridine; C_{max}, mean maximum plasma concentration; T_{max}, time to reach C_{max}; AUC, area under the curve; $t_{1/2}$, elimination half-life; TPI, tipiracil hydrochloride.
[a] Reported in reference Doi et al. [11].
[b] n = 5.
[c] AUC_{0-4}.

for patients with AGC. Based on the results of the present study, a randomised, double-blind, placebo-controlled, phase III study is ongoing (NCT02500043).

Conflict of interest statement

All authors have provided complete disclosures regarding their potential conflicts of interest. In particular, Kei Muro, Tomohiro Nishina, and Atsushi Ohtsu have received honoraria and Akihiro Sato and Shunji Takahashi have received research funding from the Taiho Pharmaceutical Company.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.04.009.

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