PHASE I STUDIES

An exploration of trifluridine/tipiracil in combination with irinotecan in patients with pretreated advanced gastric cancer

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Summary

Background. Trifluridine/tipiracil (FTD/TPI) and irinotecan are treatment options for heavily pretreated patients with advanced gastric cancer, but their efficacies are limited. We investigated the combination of FTD/TPI and irinotecan for such patients.

Methods. Patients who were refractory to fluoropyrimidine, platinum and taxane were enrolled into four cohorts (Level 1A/1B/2A/2B) and treated with irinotecan (100 [Level 1] or 125 [Level 2] mg/m² on days 1 and 15) and FTD/TPI (35 mg/m²/dose, twice daily, on days 1–5 and 8–12 [Level A] or on days 1–5 and days 15–19 [Level B]) of a 28-day cycle. The primary endpoints were the maximum tolerated dose, dose-limiting toxicities (DLTs), and recommended phase II dose (RP2D); the secondary endpoint was the disease control rate (DCR). Results. Eleven patients were enrolled: 2 at Level 1A, 3 at Level 1B, and 6 at Level 2B. DLTs occurred in 2/2 patients at Level 1A and 2/6 patients at Level 2B. Grade 3 or higher treatment-related adverse events were neutropenia (90.9%), leukopenia (54.5%), anemia (45.5%) and febrile neutropenia (18.2%). One patient at Level 2B achieved a partial response, and the DCR was 72.7% (95% CI, 39.0%-94.0%). The median progression-free survival and overall survival periods were 3.0 months (95% CI, 0.92-not reached) and 10.2 months (95% CI, 2.2-not reached), respectively. Conclusion. The RP2D of FTD/TPI combined with irinotecan was determined to be Level 1B; this level was associated with manageable hematologic toxicities and feasible non-hematologic toxicities. Further evaluation of the efficacy of RP2D treatment is necessary.

Keywords Gastric cancer · Trifluridine/tipiracil · TAS-102 · Irinotecan · CPT-11

Introduction

Although the incidence and mortality rate of gastric cancer has been decreasing dramatically over the past several decades, gastric cancer remains one of the most common malignancies throughout the world, especially in Asian countries [1]. Standard treatment for advanced gastric cancer (AGC) includes first-line fluoropyrimidine plus platinum-containing regimens, and second-line treatment has consisted of taxanes with or without ramucirumab followed by nivolumab, FTD/TPI monotherapy, or irinotecan as later-line treatments [2–8]. For HER2-positive gastric cancer, trastuzumab or trastuzumab deruxtecan is now approved for the treatment of AGC [9, 10]. Despite improvements in survival as a result of drug development for the treatment of AGC, the efficacies of such treatments remain limited, with response rates of 3.0% to 11.2% and survival periods of up to 5.7 months for third-line or later treatments [6–8].
FTD/TPI is an oral anti-cancer drug consisting of FTD (trifluridine) and TPI (tipiracil hydrochloride) combined at a molar ratio of 1:0.5 [11]. Early phase studies confirmed a dosage of 35 mg/m² b.i.d. as the recommended dose [12, 13]. FTD/TPI has also been reported to be effective against human tumor cell lines that have acquired resistance to fluoropyrimidine [14], and the clinical efficacy of FTD/TPI has already been confirmed in a phase III trial for patients with pretreated AGC refractory to fluoropyrimidine [6].

Irinotecan, a DNA topoisomerase I inhibitor, is another key drug in second- or later-line chemotherapy for patients with AGC. Recent phase III trials demonstrated that irinotecan as a second-line chemotherapy improved survival relative to best-supportive care in patients with AGC [15, 16]. In another phase III trial for second-line treatment, irinotecan demonstrated an equivalent efficacy to paclitaxel, which is used in the standard combination therapy [2]. Although several studies have reported that irinotecan monotherapy exerted a modest activity as a third-line chemotherapy for advanced gastric cancer, all evidence for later-line treatments was obtained retrospectively [8, 17].

Recently, the combination of FTD/TPI and irinotecan showed synergistic effects in an in vivo study, and the anti-tumor effect of the combination of FTD/TPI with irinotecan seemed to be the most promising, compared with monotherapy, for colorectal cancer and gastric cancer [18]. Here, we report a phase I/II study of FTD/TPI combined with a lower dose of irinotecan for the treatment of patients with advanced gastric cancer.

Patients and methods

Patient eligibility

Eligible Japanese patients were aged 20 years or more with 1) histological confirmation of advanced gastric adenocarcinoma, 2) feasible oral intake, 3) an Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1, 4) measurable lesions, 5) a disease that was refractory to fluoropyrimidine, platinum and taxane, 6) adequate organ function (absolute neutrophil count ≥ 1,500/µL, platelet count ≥ 100,000/mm³, hemoglobin level ≥ 8 g/dL, aspartate aminotransferase and alanine aminotransferase levels ≤ 2.5 times the upper limit of the normal range (ULN) without known liver metastasis or ≤ 5.0 times the ULN with known liver metastasis, total bilirubin ≤ 1.5 mg/dL, and serum creatinine ≤ 1.5 mg/dL), 7) less than grade 2 diarrhea according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 8) wild-type or single heterozygous for UGT1A1 *6 and *28, and 9) written informed consent. Patients were excluded from the study if they had a treatment history of FTD/TPI or irinotecan; serious illness such as brain metastasis, systemic infection or gastrointestinal bleeding; medical treatment such as major surgery within 4 weeks or systemic chemotherapy within 2 weeks; adverse events caused by prior chemotherapy; administration of a blood transfusion or granulocyte colony stimulating factor within 2 weeks; severe pulmonary disorder; CTCAE grade 3 or higher; or thromboembolism within 6 months.

The study was conducted at 4 centers in Japan in accordance with the International Conference of Harmonization of Good Clinical Practice Guidelines and the Declaration of Helsinki, with approval by the ethics committees/health authorities of the participating institutions (St. Marianna University School of Medicine, Chiba Cancer Center, Saitama Cancer Center, and National Hospital Organization Shikoku Cancer Center). An independent data monitoring committee (IDMC) was established with two independent experts external to this study. All patients provided their written informed consent. The UMIN Clinical Trials Registry number is UMIN000031346.

Study design and treatment

The phase I open-label dose-finding part of the study was conducted according to a 3-plus-3 design to establish the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) in patients with advanced gastric cancer to determine the recommended phase II dose (RP2D); this part was to be followed by a phase II open-label single arm part of the study to examine the efficacy and safety of the RP2D for FTD/TPI and irinotecan. Although the phase II part was initially planned as an independent cohort of patients receiving the RP2D for FTD/TPI and irinotecan, a protocol amendment was performed because of slow recruitment. As a result, the study was amended to a phase Ib study, and the phase II part was conducted to examine the efficacy and safety of FTD/TPI and irinotecan in all the enrolled patients.

Patients were enrolled at four levels, Level 1A, 1B, 2A, and 2B, and treated with an escalating dose of irinotecan and 2 dosage schedules of FTD/TPI (Fig. 1A). For the FTD/TPI dosage schedule, 35 mg/m² was administered twice daily, after the morning and evening meal. At Level A, FTD/TPI was taken on days 1–5 and days 8–12 of a 28-day treatment cycle. At Level B, it was taken on days 1–5 and days 15–19 of a 28-day treatment cycle. Irinotecan was administered by intravenous infusion over a period of at least 90 min at a dose of 100 mg/m² at Level 1 or 125 mg/m² at Level 2 on days 1 and 15 of a 28-day schedule (Fig. 1B).

Stopping or dose reductions of FTD/TPI as a result of toxicities were not allowed unless a DLT was observed during Cycle 1; thereafter, it was permitted according to prespecified criteria. Study treatment was continued until investigator-evaluated progressive disease, adverse events requiring discontinuation, a treatment-free period of > 30
consecutive days, or withdraw of consent to continue the protocol treatment.

The actual dose intensity (mg/m^2/weeks) of FTD/TPI and irinotecan was defined as the cumulative dose (mg/m^2) divided by the number of weeks from the initial treatment until discontinuation. The relative dose intensity (%) was calculated based on the initial planned dose.

**Toxicity and dose-finding procedure**

Each patient’s physical condition and laboratory test results were examined weekly. Adverse events were graded according to the National Cancer Institute’s CTCAE, version 4.03.

An event was considered to be a DLT if either of the study drugs had a possible causal relationship with the event and if the event occurred within the first 28-day treatment period and met one of the following criteria: ≥ grade 3 non-hematological toxicity (excluding nausea, vomiting and diarrhea showing improvement with supportive treatment, or ≥ grade 3 electrolyte imbalance without clinical significance); grade 4 neutropenia persisting for ≥ 8 days; ≥ grade 3 febrile neutropenia; grade 4 thrombocytopenia; or a delayed start for Cycle 2 of longer than 28 days because of adverse events.

The dose level was determined based on the observation of DLTs in at least three subjects within the same cohort who had received the investigational therapy according to the designated schedule for 28 days, as described in Fig. 1. Briefly, if 0 of the 3 patients experienced a DLT, the dose level was escalated to the next level. If 1 of the 3 patients experienced a DLT, 3 more patients were enrolled at the same dose level. The MTD was defined as the dose level at which 2 or 3 of 3 patients or at least 2 of 4 to 6 patients exhibited DLTs during the first 28-day treatment period. All DLTs, the MTD, and the RP2D were determined by the investigators and the IDMC.

**Tumor assessments and endpoints**

Imaging examinations for tumor assessments were repeated every 4 weeks until 12 weeks from the initiation of treatment or 8 weeks later. Disease assessments, including the antitumor efficacy (best overall response) and disease control rate (DCR), were evaluated based on the Response Evaluation Criteria in Solid Tumors (Revised RECIST version 1.1). PFS was calculated from the time of study enrollment until disease progression or death, and OS was calculated from the time of study enrollment until death.
Sample size and statistical analysis

The number of patients in each cohort was based on a conventional 3-plus-3 design for dose-modification studies. A maximum of 18 patients were planned to be enrolled in the phase I part. The primary analysis (and all efficacy analyses discussed herein) included the full analysis set (FAS), which was defined as eligible patients who received at least one dose each of FTD/TPI and irinotecan and in whom the presence of DLTs could be evaluated. The safety analyses included all the treated patients.

The phase II part of the study was designed to evaluate DCR. In a previous study, the DCR of irinotecan as a third-line treatment for advanced gastric cancer was 21% [19]. The DCR of FTD/TPI as a second- or third-line treatment was reported to be 51.9% [13]. Therefore, we considered a DCR of <20% to be unacceptable. Thus, since the sampling distribution for proportions actually follows a binomial distribution, we required 15 patients to evaluate a null hypothesis (a DCR of ≤30%) with a one-sided α = 0.1 and a power of 75% to detect a clinically meaningful DCR (≥55%).

Table 1  Patient characteristics

|                          | Level 1A (N=2) | Level 1B (N=3) | Level 2B (N=6) | Total (N=11) |
|--------------------------|---------------|---------------|---------------|--------------|
| Median age (range), years| 73 (58–76)    | 69 (66–76)    | 73 (61–78)    | 73 (58–78)   |
| Sex                      |               |               |               |              |
| Male                     | 2 (100.0)     | 2 (66.7)      | 6 (100.0)     | 10 (90.9)    |
| Female                   | 0 (0.0)       | 1 (33.3)      | 0 (0.0)       | 1 (9.1)      |
| ECOG performance status  |               |               |               |              |
| 0                        | 0 (0.0)       | 1 (33.3)      | 1 (16.7)      | 2 (18.2)     |
| 1                        | 2 (100.0)     | 2 (66.7)      | 5 (83.3)      | 9 (81.8)     |
| UGT1A1 polymorphism*     |               |               |               |              |
| Wild type                | 0 (0.0)       | 3 (100.0)     | 2 (33.3)      | 5 (45.5)     |
| UGT1A1*6 or UGT1A1*28    | 2 (100.0)     | 0 (0.0)       | 4 (66.7)      | 6 (54.5)     |
| Previous gastrectomy     | 0 (0.0)       | 2 (66.7)      | 2 (33.3)      | 4 (36.4)     |
| Cancer diagnosis         |               |               |               |              |
| Recurrent                | 0 (0.0)       | 2 (66.7)      | 2 (33.3)      | 4 (36.4)     |
| Metastatic               | 2 (100.0)     | 1 (33.3)      | 4 (66.7)      | 7 (63.6)     |
| Primary site             |               |               |               |              |
| Stomach                  | 1 (50.0)      | 3 (100.0)     | 4 (66.7)      | 8 (72.7)     |
| GEJ                      | 1 (50.0)      | 0 (0.0)       | 2 (33.3)      | 3 (27.3)     |
| Histological type        |               |               |               |              |
| Intestinal type          | 2 (100.0)     | 2 (66.7)      | 4 (66.7)      | 8 (72.7)     |
| Diffuse type             | 0 (0.0)       | 1 (33.3)      | 2 (33.3)      | 3 (27.3)     |
| HER2 overexpression**    | 1 (50.0)      | 0 (0.0)       | 1 (16.7)      | 2 (18.2)     |
| Previous treatment lines |               |               |               |              |
| 2                        | 2 (100.0)     | 3 (100.0)     | 4 (66.7)      | 9 (81.8)     |
| 3                        | 0 (0.0)       | 0 (0.0)       | 2 (33.3)      | 2 (18.2)     |
| Prior immunotherapy      | 1 (50.0)      | 1 (33.3)      | 2 (33.3)      | 4 (36.4)     |

*None of the patients had homozygous or double heterozygous variations
**Immunohistochemistry score of 3 or positive for in situ hybridization

Results

Patient characteristics

From September 2018 to November 2019, eleven patients were enrolled and treated: 2 at Level 1A, 3 at Level 1B and 6 at Level 2B. All eligible patients were included in the FAS population and the safety analysis. Table 1 shows the backgrounds of all eleven patients enrolled in this study. The majority of patients were male, with an age range of 58 to 78 years old. Nine patients (81.8%) had a performance status (PS) of 1, and 2 patients (18.2%) had a PS of 0. Six patients (54.4%; 2 in Level 1A, 4 in Level 2B) were heterozygous for UGT1A1 polymorphisms *6 or *28; the remaining patients had the wild-type. Four patients (36.4%; 2 in Level 1B, 2 in Level 2B) had received a gastrectomy. Four patients (36.4%) had recurrent disease, and 7 patients (63.6%) had unresectable disease. Most of the patients (81.8%) had a history of two previous lines of treatment, and 4 patients (36.4%) had a history of
prior immunotherapy use. Nine of the 11 patients (81.8%) received post-treatment.

**FTD/TPI and irinotecan administration**

Among the 11 patients who received at least one dose of both FTD/TPI and irinotecan according to the protocol treatment, the median relative dose intensity of FTD/TPI during the first cycle was 82.5%, 100.0%, and 70.0% at Level 1A, 1B, and 2B, respectively. For all treatment periods, the median relative dose intensities of FTD/TPI/irinotecan were 82.5%/75.0% at Level 1A, 95.5%/33.3% at Level 1B, and 89.8%/62.1% at Level 2B. The median FTD/TPI treatment duration was 62 days (10.5 days, 81 days, and 75.5 days at Level 1A, 1B, and 2B, respectively). The median irinotecan treatment duration was 57 days (11 days, 2 days, and 70.5 days at Level 1A, 1B, and 2B, respectively). Treatment was discontinued in 9 of the 11 patients because of progressive disease and in 2 of the 11 patients because of patient requests that were unrelated to adverse events.

**DLTs and RP2D**

As described in Table 2, both patients (100.0%) treated at Level 1A experienced DLTs (Grade 3 gum infection and Grade 3 febrile neutropenia). Febrile neutropenia was also reported in a patient treated at Level 1A at a time point beyond the DLT evaluation period (Day 29); the IDMC determined this to be an adverse event corresponding to a DLT. No DLTs were observed at Level 1B. At Level 2B, 2 of the 6 (33.3%) patients at experienced DLTs (Grade 3 mucositis oral and Grade 3 febrile neutropenia). After discussion with the IDMC, Level 1B was determined to be the RP2D based on the serious adverse events that occurred during second or later treatment courses, as described below.

**Safety and tolerability**

All 11 patients who received at least one dose of both FTD/TPI and irinotecan and were included in the safety evaluation experienced at least one treatment-related adverse event. The common treatment-related adverse events are summarized in Table 3. Comparing Level 1A and 1B, the schedule modification for FTD/TPI led to a lower frequency of adverse events related to hematological toxicities, including anemia, white blood cell reductions, neutropenia, and febrile neutropenia. However, the dose increase for irinotecan (from Level 1A to 1B) led to an increased frequency of gastrointestinal toxicities, such as mucositis, diarrhea, and gum infection. Table 3 provides a detailed summary of the most common treatment-related adverse events encountered across all cycles.

| **Table 2** Profiles of each dose levels |
|-----------------------------------------|
| **Level 1A** N=2                        | **Level 1B** N=3 | **Level 2B** N=6 |
| Number of courses, median (range)      | 1 (1–1)         | 3 (2–3)         | 3 (1–5)         |
| DLTs, N (%)                            | 2 (100.0)       | 0 (0.0)         | 2 (33.3)        |
| Description of DLTs                   | Gum infection   | Mucositis       | Febrile neutropenia |
|                                        | Febrile neutropenia |           |                  |

| **Table 3** Most common treatment-related adverse events (all cycles) |
|---------------------------------------------------------|------------------|
| **Level 1A (N=2)**                                      | **Level 1B (N=3)** | **Level 2B (N=6)** |
| All grades G3/4                                         | All grades G3/4  | All grades G3/4  |
| N (%)                                                  | N (%)            | N (%)            |
| Hematological toxicities                               |                  |                  |
| Neutropenia                                            | 2 (100.0)        | 3 (100.0)        | 6 (100.0)       |
| Reduced white blood cell count                         | 2 (100.0)        | 3 (100.0)        | 5 (83.3)        |
| Anemia                                                 | 2 (100.0)        | 2 (100.0)        | 3 (50.0)        |
| Reduced platelet count                                 | 0 (0)            | 1 (33.3)         | 4 (66.7)        |
| Reduced lymphocyte count                               | 1 (50.0)         | 0 (0)            | 2 (33.3)        |
| Febrile neutropenia                                    | 1 (50.0)         | 0 (0)            | 1 (16.7)        |
| Non-hematological toxicities                           |                  |                  |
| Appetite loss                                          | 1 (50.0)         | 2 (66.7)         | 5 (83.3)        |
| Diarrhea                                               | 1 (50.0)         | 2 (66.7)         | 2 (33.3)        |
| Constipation                                           | 1 (50.0)         | 0 (0)            | 3 (50.0)        |
| Fatigue                                                | 0 (0)            | 3 (100.0)        | 1 (16.7)        |
| Mucositis                                              | 0 (0)            | 1 (33.3)         | 2 (33.3)        |
| Gum infection                                          | 1 (50.0)         | 0 (0)            | 0 (0)           |
| Peritoneal infection                                   | 0 (0)            | 1 (33.3)         | 0 (0)           |
| Increased γ-glutamyl transpeptidase level              | 0 (0)            | 0 (0)            | 1 (16.7)        |
| Increased blood bilirubin level                        | 0 (0)            | 0 (0)            | 1 (16.7)        |
Level 1B to Level 2B) resulted in an increase in hematological toxicities.

No treatment-related deaths occurred in this study. Serious adverse events (SAE) occurred in 1 patient (gingival infection) treated at Level 1A, in 1 patient (peritoneal infection) treated at Level 1B, and in 2 patients (reduced neutrophil count, reduced platelet count, and febrile neutropenia) treated at Level 2B; all events other than the peritoneal infection that occurred in 1 patient treated at Level 1B were considered to be related to treatment with FTD/TPI and irinotecan.

Efficacy

The DCR was 72.7% (95% confidence interval [CI], 39.0%-94.0%) (Table 4). When analyzed according to level, the DCR was 50.0% at Level 1A, 66.7% at Level 1B, and 83.3% at Level 2B. The response rate was 9.1% overall and 16.7% at Level 2B. None of the patients treated at Level 1A or Level 1B achieved a response. The overall median PFS was 3.0 months (95% CI, 2.8 months to NA), and the overall median OS was 10.2 months (95% CI, 6.3 to NA).

Discussion

To our best knowledge, this is the first report to evaluate the combination of FTD/TPI and irinotecan in patients with refractory advanced gastric cancer. The hematologic toxicities could be managed by modifying the schedule of FTD/TPI to biweekly dosing, with feasible non-hematologic toxicities.

Table 4 Efficacy summary

|                  | Level 1A (N=2) | Level 1B (N=3) | Level 2B (N=6) | Total (N=11) |
|------------------|----------------|----------------|---------------|--------------|
| N (%)            | N (%)          | N (%)          | N (%)         | N (%)        |
| CR               | 0 (0.0)        | 0 (0.0)        | 0 (0.0)       | 0 (0.0)      |
| PR               | 0 (0.0)        | 0 (0.0)        | 1 (16.7)      | 1 (9.1)      |
| SD               | 1 (50.0)       | 2 (66.7)       | 4 (66.7)      | 7 (63.6)     |
| PD               | 1 (50.0)       | 1 (33.3)       | 1 (16.7)      | 3 (27.3)     |
| NE               | 0 (0.0)        | 0 (0.0)        | 0 (0.0)       | 0 (0.0)      |
| Response rate (CR + PR) (%) | 0.0 [0.0–84.1] | 0.0 [0.0–70.8] | 16.7 [0.4–64.1] | 9.1 [0.2–41.3] |
| Disease control rate (CR + PR + SD) (%) | 50.0 [1.3–98.7] | 66.6 [9.4–99.2] | 83.3 [35.9–99.6] | 72.7 [39.0–94.0] |

CI confidence interval, CR complete response, NE not evaluable, PD progressive disease, PR partial response, SD stable disease

A phase I trial for the dose-escalation of FTD/TPI combined with irinotecan has been conducted for patients with pretreated metastatic colorectal cancer [18, 20, 21]. The recommended dose was determined as 25 mg/m² b.i.d. of FTD/TPI with biweekly irinotecan (150 mg/m²), but a higher frequency and more severe hematologic toxicities were observed, compared with FTD/TPI monotherapy or other irinotecan-containing regimens. Although a biomarker for FTD/TPI efficacy has yet to be identified, previous studies have suggested the presence of a direct correlation between the dose of FTD/TPI and the antitumor effect [12, 22, 23]. Thus, the development of a combination therapy using the full dose of 35 mg/m² of FTD/TPI remains an option. Regarding the schedule for FTD/TPI, a biweekly FTD/TPI schedule in patients with pretreated mCRC has already been shown to have an equivalent efficacy and lower toxicity than the current schedule of FTD/TPI [24, 25]. On the other hand, irinotecan showed its noninferiority at a dose of 125 mg/m² to 150 mg/m² in terms of progression-free survival when administered in combination with the anti-metabolites 5-fluorouracil or tegafur/gimeracil/oteracil in a phase III trial for patients with metastatic colorectal cancer [26]. These results indicated that a dosage of 35 mg/m² of FTD/TPI combined with a lower dose of irinotecan improved the efficacy while decreasing toxicities for the treatment of patients with advanced gastric cancer. Considering the toxicities observed at Level 1B and 2B, our results suggest the possible value of schedule modification for the treatment of patients with advanced gastric cancer to improve the insufficient dose intensity of FTD/TPI.

In a preclinical study, the combination of FTD/TPI and irinotecan demonstrated synergistic effects, and the antitumor effect of the combination of FTD/TPI with irinotecan seemed to be the most promising, compared with monotherapy, for the treatment of colorectal cancer and gastric cancer [18]. SN-38, which is an active metabolite of irinotecan, reportedly induces DNA strand breaks and increases G2/M arrest when used in combination with FTD [20]. Other studies have shown that FTD/TPI is also effective against human tumor cell lines that have acquired resistance to 5-FU [14]. Actually, the combination of FTD/TPI plus irinotecan produced favorable tumor responses in patients with metastatic colorectal cancer or gastrointestinal tumors who were refractory to previous treatments, including fluoropyrimidine and oxaliplatin [21, 25]. In the present study, the combination of FTD/TPI and irinotecan showed a promising DCR of 72.7% in patients with advanced gastric cancer refractory to fluoropyrimidine, platinum, and taxane; this DCR was comparable to the rates for FTD/TPI monotherapy, irinotecan monotherapy, and nivolumab [6, 7, 27, 28].

Our study was limited by the insufficient number of patients with heavily treated advanced gastric cancer. Initially, we planned a phase II study to examine the efficacy...
and safety of the RP2D of FTD/TPI and irinotecan. Because of the slow enrollment, however, we had to amend the protocol for the phase II study to include all the enrolled patients. In this study, we reported a promising efficacy: the DCR of 72.7% and the lower 95% CI of 39.0% allowed the null-hypothesis to be rejected. Because of the insufficient number of patients who received the RP2D and the short PFS of 3.0 months, however, we cannot conclude that this regimen is effective. Although both FTD/TPI and irinotecan have been approved for the treatment of advanced gastric cancer and the safety of this combination has been reported for the treatment of metastatic colorectal cancer [21], further evaluation exploring the safety and efficacy at the RP2D is necessary.

In conclusion, the RP2D of FTD/TPI in combination with irinotecan was determined to be Level 1B, corresponding to 35 mg/m²/dose of FTD/TPI administered twice daily on days 1–5 and days 15–19 of a 28-day cycle and 100 mg/m² of irinotecan on days 1 and 15. The combination of FTD/TPI and irinotecan showed promising disease control in patients with advanced gastric cancer refractory to fluoropyrimidine, platinum, and taxane.

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Author contributions All authors contributed to the study conception and design. Patient recruitment was performed by Takuro Mizukami, Keiko Minashi, Hiroki Hara, Tomohiro Nishina, Yusuke Amanuma, Naoki Takahashi, Akio Nakasha, Masaki Takahashi, and Takako Eguchi Nakajima. Data collection and analysis were performed by Masaki Takahashi. The first draft of the manuscript was written by Takuro Mizukami and Takako Eguchi Nakajima. All authors revised and approved the final manuscript.

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

Declarations

Ethics approval All considerations regarding the protection of human subjects were performed in accordance with the ICH Harmonized Guidelines for Good Clinical Practice, the ethical principles of which originate from the Declaration of Helsinki, and all applicable regulatory requirements.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

Conflict of interest Dr. Mizukami reports grants and personal fees from Taiho Pharmaceutical, Eli Lilly Japan, and Ono pharmaceutical as well as personal fees from Otsuka Pharmaceutical Factory, Asahi Kasei Pharmaceutical, Merck Biopharma, Sanofi, and Takeda Pharmaceutical. Dr. Hara grants, and personal fees from Bayer, Chugai, Daiichi Sankyo, Merck Biopharma, MSD, Ono, and Taiho, as well as grants from Astellas, AstraZeneca, BeiGene, Boehringer Ingelheim, Dainippon Sumitomo, Eisai, Elevar Therapeutics, GSK, Incyte, Pfizer, personal fees from Bristol-Myers Squibb, Lilly, Sanofi, and Yakult. Dr. Nakajima reports grants and personal fees from Taiho Pharmaceutical Co., Sumitomo Dainippon Pharma Co., Ono Pharmaceutical Co., Amgen, Takeda Pharmaceutical Co., Chugai Pharmaceutical Co., Sanofi K.K., Nippon Kayaku Co., MSD K.K., Eli Lilly Japan K.K., Daiichi Sankyo Co., Merck Serono Co. as well as a grant from Eisai Co., and personal fees from Boehringer Ingelheim, Bristol-Myers Squibb, Novartis Japan, Bayer Yakuhin, Pfizer Japan Inc., Yakult Honsha Co., Nipro Co, Celltrion Healthcare Japan, Teijin Pharma, Sawai Pharmaceutical Co., Drs. Minashi, Nishina, Amanuma, Naoki Takahashi, Nakayama, Masaki Takahashi, and have nothing to disclose.

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