An Exploration of Trifluridine/Tipiracil in Combination with Irinotecan in Patients with Pretreated Advanced Gastric Cancer

Takuro Mizukami
St Marianna University School of Medicine: Sei Marianna Ika Daigaku https://orcid.org/0000-0002-9960-5629

Keiko Minashi
Chiba Cancer Center: Chiba-ken Gan Center

Hiroki Hara
Saitama Cancer Center

Tomohiro Nishina
Shikoku Cancer Center: Kokuritsu Byoin Shikoku Gan Center

Yusuke Amanuma
Chiba Cancer Center: Chiba-ken Gan Center

Naoki Takahashi
Saitama Cancer Center

Akio Nakasya
Shikoku Cancer Center: Kokuritsu Byoin Shikoku Gan Center

Masaki Takahashi
St Marianna University School of Medicine: Sei Marianna Ika Daigaku

Takako Eguchi Nakajima (tnakajima@kuhp.kyoto-u.ac.jp)
Kyoto University Graduate School of Medicine Faculty of Medicine: Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu https://orcid.org/0000-0002-4589-2335

Research Article

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

Posted Date: December 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1143619/v1

Version of Record: A version of this preprint was published at Investigational New Drugs on March 12th, 2022. See the published version at https://doi.org/10.1007/s10637-022-01223-9.

Abstract

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

Methods: Patients who refractory to fluoropyrimidine, platinum and taxane were enrolled into four cohorts (Level 1A/1B/2A/2B) used an escalated dose of irinotecan [100 (Level 1) or 125 mg/m^2 (Level 2) on days 1 and 15] with 2 schedules of FTD/TPI 35 mg/m^2/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 and secondary objectives were determination of maximum tolerated dose, dose-limiting toxicities (DLTs), and recommended phase II dose (RP2D) , and evaluation of disease control rate (DCR), respectively.

Results: Eleven patients were enrolled; 2 at Level 1A, 3 at Level 1B and 6 at Level 2B. DLTs occurred in 2/2 patient 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 partial response and the DCR was 72.7% (95% CI 39.0- 94.0%). The median progression-free survival and overall survival was 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 with manageable hematologic toxicities and feasible non-hematologic toxicities. Further evaluation for its efficacy in the RP2D is necessary.

Mini-abstract: A phases Ib study of trifluridine/tipiracil in combination with irinotecan for advanced gastric cancer determined the recommended dose with manageable hematologic toxicities and feasible non-hematologic toxicities.

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 treatment (2-8). For HER2 positive gastric cancer, trastuzumab or trastuzumab deruxtecan is now approved for treatment of advanced gastric cancer (9, 10). Despite our efforts of drug development against AGC have improved the survival, the efficacy is limited with the response rate of 3.0 to 11.2 % and the survival of up to 5.7 months in 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 the dosage of 35 mg/m^2 b.i.d.

was defined as recommended dose (12, 13). FTD/TPI have been reported to be also effective against human tumor cell lines which acquired resistance to fluoropyrimidine (14), and it's clinical efficacy had 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 chemotherapy for patients with AGC. Recent phase III trials demonstrated that irinotecan as second-line chemotherapy improved in terms of survival relative to best supportive care in patients with AGC (15, 16). In another phase III trial for second-line treatment, irinotecan demonstrated the equivalent efficacy to paclitaxel constituting the standard combination therapy (2). Although several studies reported that irinotecan monotherapy had modest activity as third-line chemotherapy for advanced gastric cancer in third-line treatment, all evidences were performed retrospectively in later-line treatment (8, 17).

Recently, combination of FTD/TPI and irinotecan demonstrated synergistic effects in vivo study, and the antitumor effect of combination of FTD/TPI with irinotecan seemed the most promising compared with monotherapy in colorectal cancer and gastric cancer (18). Here, we report phase I/II study of FTD/TPI combined with lower dose of irinotecan for treatment of patients with advanced gastric cancer.

Patients And Methods

Patient eligibility

Eligible patients are aged 20 years or more Japanese with: 1) histological confirmation of advanced gastric adenocarcinoma; 2) patient with oral intake; 3) Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1; 4) patients with measurable lesions; 5) disease refractory to fluoropyrimidine, platinum and taxane; 6) adequate organ function (Absolute neutrophil count ≥ 1,500/μL, platelet counts ≥ 100,000/mm^3, hemoglobin levels ≥ 8.0 g/dL, aspartate aminotransferase and alanine aminotransferase ≤ 2.5 times the upper limit of normal range [ULN] without known liver metastasis or ≤ 5.0 times the ULN with known liver metastasis, total bilirubin ≤ 1.5 mg/dL, Serum creatinine ≤ 1.5 mg/dL); 7) less than grade 2 of diarrhea according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 8) UGT1A1 gene *6*28 wild type or single hetero; 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, systemic chemotherapy within 2 weeks; adverse events due to prior chemotherapy; administration of blood transfusion or granulocyte colony stimulating factor within 2 weeks; severe pulmonary disorder; CTCAE grade 3 or higher of thromboembolism within 6 months.

The study was conducted 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 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). Independent data monitoring committee (IDMC) was established with two independent experts external to this study. All patients provided their written informed consent. UMIN Clinical Trials Registry: UMIN000031346.

Study design and treatment

The phase I open-label dose finding part was conducted according to 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), followed by the phase II open-label single arm part to examine the efficacy and safety of RP2D of FTD/TPI and irinotecan. Although the phase II part was initially planned as a dependent cohort of patients receiving RP2D of FTD/TPI and irinotecan, the protocol amendment was performed due to slow recruitment. Finally, this 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 enrolled patients.

Patients were enrolled gradually into four levels, Level 1A, 1B, 2A, and 2B, used a deescalated dose of irinotecan with 2 dosage schedules of FTD/TPI (Figure 1A). Regarding FTD/TPI, 35 mg/m^2 were administered twice daily, after the morning and evening meal. At level A, taken on days 1–5 and days 8–12 of each 28-day treatment cycle. And at level B, taken on days 1–5 and days 15-19 of each 28-day treatment cycle. Irinotecan, 100 mg/m^2 at level 1 or 125 mg/m^2 at level 2, was administered by intravenous infusion over at least 90 min on days 1 and 15 in a 28-day schedule (Figure 1B).

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

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

Toxicity and dose-finding procedure

Examination of patient's condition and laboratory tests were repeated weekly. Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

An event was considered a dose limiting toxicity if it has a possible causal relationship to study drugs and occurs within the first 28-day treatment period of protocol treatment and meets one of following criteria: ≥ grade 3 non-hematological toxicities (excluding nausea, vomiting and diarrhea showing

improvement with supportive treatment, or ≥ grade 3 electrolyte imbalance without clinically significance); grade 4 neutropenia persisting for ≥ 8 days; ≥ grade 3 febrile neutropenia; grade 4 thrombocytopenia; or delay of starting Cycle 2 longer than 28 days due to adverse events.

Dose level was determined based on observed DLTs from at least three subjects in the same cohort who have received investigational therapy according to the designated schedule for 28 days as described in **Figure 1**. Briefly, if 0 of the 3 patients experienced a DLT, the dose level was escalated to next level. if 1 out 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 more of 3 patients, or at least 2 of 4 to 6 patients, had DLTs during the first 28-day treatment period. All DLTs, MTD, and RP2D was finally judged by the investigators and the IDMC.

Tumor assessments and endpoints

Imaging examination for tumor assessment repeated every 4 weeks until 12 weeks from initiation of treatment or 8weeks later. Disease assessment, including the antitumor efficacy (best overall response), disease control rate (DCR) was evaluated based on response evaluation criteria in solid tumors (Revised RECIST version 1.1). PFS was calculated from enrollment to disease progression or death and OS was calculated from enrollment to 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 treated with FTD/TPI and irinotecan at least each one dose who could be evaluated for DLT. The safety analyses included all treated patients.

The phase II part of the study was designed to evaluate DCR. In the previous study, it was reported that DCR of irinotecan third-line treatment in advanced gastric cancer patients was 21 % (19). It was also reported that DCR of FTD/TPI as second- or third-line treatment was 51.9 % (13). Therefore, we considered a DCR of <20 % to be unacceptable. Thus, based on 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 $\alpha = 0.1$ and of power of 75 % to detect a clinically meaningful DCR (≥55 %).

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 background of the all eleven patients enrolled to 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. Heterozygotes for the UGT1A1 polymorphisms *6 or *28 were detected in 6 patients (54.5 %), 2 and 4 patients at Level 1A and 2B, respectively, while the other patients had the wildtype. Gastrectomy had performed in 4 patients (36.4 %), 2 and 2 patients at Level 1B and 2B, respectively. 4 patients (36.4 %) had recurrent disease, and 7 patients (63.6 %) had unresectable disease. Most patients (81.8 %) had history of 2 previous treatment lines and 4 patients (36.4 %) had history of prior immunotherapy use. Nine of 11 patients (81.8%) received post-treatment.

FTD/TPI and irinotecan administration

In the 11 treated patients with at least each one dose administration of 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. Regarding during all treatment periods, the median relative dose intensity of FTD/TPI or irinotecan was 82.5 %/ 75.0 %, 95.5 %/ 33.3 %, and 89.8 %/ 62.1 % at Level 1A, 1B and 2B, respectively. 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 11 patients because of progressive disease, and 2 of 11 patients because of patients' requests unrelated to the adverse events.

DLTs and RP2D

Two of 2 (100.0 %) patient at Level 1A experienced the DLTs (Grade 3 gum infection and Grade 3 febrile neutropenia). Febrile neutropenia was reported in another patient in Level 1A beyond the DLT evaluation period (Day 29), and it was determined an adverse event corresponding to DLT by the IDMC. The dose level was moved to next Level 1B and no DLTs were observed at Level 1B. Two of 6 (33.3 %) patients at Level 2B experienced DLTs (Grade 3 mucositis oral and Grade 3 febrile neutropenia). As a result of the discussion with IDMC, Level 1B was determined to be RP2D referring to serious adverse events that occurred in the second course or later as described below.

Safety and tolerability

All 11 patients were evaluable for safety who received FTD/TPI and irinotecan experienced at least one treatment-related adverse event. The common treatment-related adverse events are summarized in **Table 2**. Comparing Level 1A and 1B, the schedule modification of FTD/TPI led to decrease frequency of adverse events relating hematological toxicities including anemia, white blood cell decreased, neutropenia, and febrile neutropenia. However, the dose elevation of irinotecan (Level 1B to Level 2B) resulted in increase of hematological toxicities.

No treatment-related death occurred in this study. Serious adverse events (SAE) occurred in 1 patient (gingival infection) in Level 1A, 1 patient (peritoneal infection) in Level 1B, and 2 patients (neutrophil count decreased, platelet count decreased, and febrile neutropenia) in Level 2B, and all events other than

peritoneal infection that occurred in 1 patient in Level 1B were considered related to FTD/TPI and irinotecan.

Efficacy

The DCR was 72.7% (95% confidence interval [CI], 39.0- 94.0 %) (**Table 3**). When analyzed by level, it was 50.0% at Level 1A, 66.7% at Level 1B, and 83.3% at Level 2B. The response rate was 9.1% in all patients and 16.7% at Level 2B. No patients achieved a response in Level 1A and Level 1B. Median PFS was 3.0 months (95 % CI was 2.8 to NA months) and the OS was 10.2 months (95% CI was 6.3 to NA) overall.

Discussion

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

A phase I trial for dose-escalation of FTD/TPI combined with irinotecan was conducted for the patients with pretreated metastatic colorectal cancer (18, 20, 21). The recommended dose was determined as 25 mg/m^2 b.i.d. of FTD/TPI with biweekly 150 mg/m^2 of irinotecan with higher frequency and more severe hematologic toxicities than FTD/TPI monotherapy or other irinotecan containing regimens. Although the investigation of the biomarker for FTD/TPI is still in progress, previous studies suggest that the presence of direct correlation between the dose of FTD/TPI and the antitumor effect (12, 22, 23). Thus, there was still room for developing the combination therapy with the full dosage of 35 mg/m^2 of FTD/TPI. Regarding the schedule of FTD/TPI, a biweekly FTD/TPI schedule in patients with pretreated mCRC has already shown equivalent efficacy with less toxicity compared with the current schedule of FTD/TPI (24, 25). On the other hand, irinotecan showed its noninferiority of 125 mg/m^2 to 150 mg/m^2 in terms of progression-free survival when given combination with antimetabolites, 5-fluorouracil or tegafur/gimeracil/oteracil, in a phase III trial for patients with metastatic colorectal cancer (26). These results indicated that the dosage of 35 mg/m^2 of FTD/TPI combined with lower dose of irinotecan improve the efficacy with decreasing toxicities for treatment of patients with advanced gastric cancer. Considering the toxicities at Level 1B and 2B, our results succussed to indicated the value of schedule modification for treatment of patients with advanced gastric cancer to improve in insufficient dose intensity of FTD/TPI.

In a preclinical study, combination of FTD/TPI and irinotecan demonstrated synergistic effects, and the antitumor effect of combination of FTD/TPI with irinotecan seemed the most promising compared with monotherapy in colorectal cancer and gastric cancer (18). It was reported that SN-38, an active metabolite of irinotecan, induces DNA strand breaks and G2/M arrest is increased in combination with FTD (20). Other studies showed that FTD/TPI is also effective against human tumor cell lines which acquired resistance to 5-FU (14). Actually, the combination of FTD/TPI plus irinotecan showed favorable tumor response in patients with metastatic colorectal cancer or gastrointestinal tumor who were

refractory to previous treatment including fluoropyrimidine and oxaliplatin (21, 25). In this study, the combination of FTD/TPI and irinotecan showed promising disease control rate of 72.7 % in patient with advanced gastric cancer refractory to fluoropyrimidine, platinum, and taxane, which was considerably comparable to that of FTD/TPI monotherapy, irinotecan monotherapy or nivolumab (6, 7, 27, 28).

Our study had a limitation of an insufficient number of patients with heavily-treated advanced gastric cancer. Initially, we planned the phase II part to examine the efficacy and safety of RP2D of FTD/TPI and irinotecan. However, we conducted the protocol amendment of the phase II part evaluating in all enrolled patients due to slow enrollment. In this study, we reported the promising efficacy, 72.7 % DCR with 39.0 % lower limit of 95 % confidence interval rejecting null-hypothesis. Because of insufficient number of patients totally and patients received the dose of RP2D, we cannot conclude this regimen is effective. Further evaluation to explore its efficacy in the RP2D is necessary.

In conclusion, the RP2D of FTD/TPI in combination with irinotecan was determined to be Level 1B, 35 mg/m^2/dose of FTD/TPI, twice daily, on days 1-5 and days 15-19 of a 28-day cycle with 100 mg per square of irinotecan on days 1 and 15. The combination of FTD/TPI and irinotecan showed promising disease control in patient with advanced gastric cancer refractory to fluoropyrimidine, platinum, and taxane.

Declarations

Funding: This investigation was funded by TAIHO PHARMACEUTICAL CO., LTD.

Conflict of Interest:

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

Ethics approval: All considerations regarding the protection of human subjects be carried out in accordance with the protocol, ICH Harmonized Guidelines for Good Clinical Practice, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements.

Consent for publication: Not applicable

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, 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 it and approved the final manuscript.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. Epub 2018/09/13. doi: 10.3322/caac.21492. PubMed PMID: 30207593.
2. Hironaka S, Ueda S, Yasui H, Nishina T, Tsuda M, Tsumura T, et al. Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2013;31(35):4438-44. Epub 2013/11/06. doi: 10.1200/JCO.2012.48.5805. PubMed PMID: 24190112.
3. Wilke H, Muro K, Van Cutsem E, Oh SC, Bodoky G, Shimada Y, et al. Ramucirumab plus paclitaxel versus placebo plus paclitaxel in patients with previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (RAINBOW): a double-blind, randomised phase 3 trial. The lancet oncology. 2014;15(11):1224-35. Epub 2014/09/23. doi: 10.1016/S1470-2045(14)70420-6. PubMed PMID: 25240821.
4. Shitara K, Takashima A, Fujitani K, Koeda K, Hara H, Nakayama N, et al. Nab-paclitaxel versus solvent-based paclitaxel in patients with previously treated advanced gastric cancer (ABSOLUTE): an open-label, randomised, non-inferiority, phase 3 trial. The lancet Gastroenterology & hepatology. 2017;2(4):277-87. Epub 2017/04/14. doi: 10.1016/S2468-1253(16)30219-9. PubMed PMID: 28404157.
5. Bando H, Shimodaira H, Fujitani K, Takashima A, Yamaguchi K, Nakayama N, et al. A phase II study of nab-paclitaxel in combination with ramucirumab in patients with previously treated advanced gastric cancer. Eur J Cancer. 2018;91:86-91. Epub 2018/01/22. doi: 10.1016/j.ejca.2017.11.032. PubMed PMID: 29353164.
6. Shitara K, Doi T, Dvorkin M, Mansoor W, Arkenau HT, Prokharau A, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. The lancet oncology. 2018;19(11):1437-48. Epub 2018/10/26. doi: 10.1016/S1470-2045(18)30739-3. PubMed PMID: 30355453.
7. Kang YK, Boku N, Satoh T, Ryu MH, Chao Y, Kato K, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017;390(10111):2461-71. Epub 2017/10/11. doi: 10.1016/S0140-6736(17)31827-5. PubMed PMID: 28993052.
8. Nishimura T, Iwasa S, Nagashima K, Okita N, Takashima A, Honma Y, et al. Irinotecan monotherapy as third-line treatment for advanced gastric cancer refractory to fluoropyrimidines, platinum, and taxanes. Gastric Cancer. 2017;20(4):655-62. Epub 2016/11/20. doi: 10.1007/s10120-016-0670-9. PubMed PMID: 27858180.
9. Shitara K, Bang YJ, Iwasa S, Sugimoto N, Ryu MH, Sakai D, et al. Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer. N Engl J Med. 2020;382(25):2419-30. Epub

2020/05/30. doi: 10.1056/NEJMoa2004413. PubMed PMID: 32469182.

10. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687-97. Epub 2010/08/24. doi: 10.1016/S0140-6736(10)61121-X. PubMed PMID: 20728210.
11. Emura T, Nakagawa F, Fujioka A, Ohshimo H, Yokogawa T, Okabe H, et al. An optimal dosing schedule for a novel combination antimetabolite, TAS-102, based on its intracellular metabolism and its incorporation into DNA. Int J Mol Med. 2004;13(2):249-55. Epub 2004/01/14. PubMed PMID: 14719131.
12. Doi T, Ohtsu A, Yoshino T, Boku N, Onozawa Y, Fukutomi A, et al. Phase I study of TAS-102 treatment in Japanese patients with advanced solid tumours. Br J Cancer. 2012;107(3):429-34. Epub 2012/06/28. doi: 10.1038/bjc.2012.274. PubMed PMID: 22735906; PubMed Central PMCID: PMCPMC3405214.
13. Bando H, Doi T, Muro K, Yasui H, Nishina T, Yamaguchi K, et al. A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201). Eur J Cancer. 2016;62:46-53. Epub 2016/05/23. doi: 10.1016/j.ejca.2016.04.009. PubMed PMID: 27208903.
14. Emura T, Murakami Y, Nakagawa F, Fukushima M, Kitazato K. A novel antimetabolite, TAS-102 retains its effect on FU-related resistant cancer cells. International journal of molecular medicine. 2004;13(4):545-9. Epub 2004/03/11. PubMed PMID: 15010854.
15. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer–a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur J Cancer. 2011;47(15):2306-14. Epub 2011/07/12. doi: 10.1016/j.ejca.2011.06.002. PubMed PMID: 21742485.
16. Kang JH, Lee SI, Lim DH, Park KW, Oh SY, Kwon HC, et al. Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2012;30(13):1513-8. Epub 2012/03/14. doi: 10.1200/JCO.2011.39.4585. PubMed PMID: 22412140.
17. Makiyama A, Arimizu K, Hirano G, Makiyama C, Matsushita Y, Shirakawa T, et al. Irinotecan monotherapy as third-line or later treatment in advanced gastric cancer. Gastric Cancer. 2018;21(3):464-72. Epub 2017/08/12. doi: 10.1007/s10120-017-0759-9. PubMed PMID: 28799048.
18. Nukatsuka M, Nakagawa F, Saito H, Sakata M, Uchida J, Takechi T. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS-102, with irinotecan hydrochloride on human colorectal and gastric cancer xenografts. Anticancer research. 2015;35(3):1437-45. Epub 2015/03/10. PubMed PMID: 25750295.
19. Takashi Nishimura SI, Kengo Nagashima, Natsuko Okita, Atsuo Takashima, Yoshitaka Honma, Ken Kato, Tetsuya Hamaguchi, Yasuhide Yamada, Yasuhiro Shimada, Narikazu Boku. Irinotecan

monotherapy as third-line treatment for advanced gastric cancer refractory to fluoropyrimidines, platinum, and taxanes. Gastric cancer : official journal of the International Gastric Cancer Association and the Japanese Gastric Cancer Association. 2014. Epub 2016 Nov 17. [Epub ahead of print].

20. Temmink OH, Hoebe EK, Fukushima M, Peters GJ. Irinotecan-induced cytotoxicity to colon cancer cells in vitro is stimulated by pre-incubation with trifluorothymidine. Eur J Cancer. 2007;43(1):175-83. Epub 2006/10/20. doi: 10.1016/j.ejca.2006.08.022. PubMed PMID: 17049227.
21. Doi T, Yoshino T, Fuse N, Boku N, Yamazaki K, Koizumi W, et al. Phase I study of TAS-102 and irinotecan combination therapy in Japanese patients with advanced colorectal cancer. Investigational new drugs. 2015;33(5):1068-77. Epub 2015/07/15. doi: 10.1007/s10637-015-0271-1. PubMed PMID: 26163340; PubMed Central PMCID: PMC4768213.
22. Tomohiro Nishina TY ES, Kentaro Yamazaki, Yoshito Komatsu, Hideo Baba, Akihito Tsuji, Kensei Yamaguchi, Kei Muro, Naotoshi Sugimoto, Yasushi Tsuji, Toshikazu Moriwaki, Taito Esaki, Chikuma Hamada, Takanori Tanase, Atsushi Ohtsu. Onset of neutropenia as an indicator of treatment response in the randomized phase II of TAS-102 vs placebo in Japanese patients with metastatic colorectal cancer (Study J003-10040030). J Clin Oncol 34, 2016 (suppl; abstr 3557) 2016.
23. Atsushi Ohtsu TY AF, Rocio Garcia-Carbonero, Guillem Argiles, Alberto F. Sobrero, Marc Peeters, Lukas Makris, Fabio Benedetti, Alberto Zaniboni, Yasuhiro Shimada, Kentaro Yamazaki, Yoshito Komatsu, Howard S. Hochster, Heinz-Josef Lenz, Ben Tran, Mona Wahba, Kenichiro Yoshida, Eric Van Cutsem, Robert J. Mayer. Onset of neutropenia as an indicator of treatment response in the phase III RECOURSE trial of TAS-102 vs placebo in patients with metastatic colorectal cancer. J Clin Oncol 34, 2016 (suppl; abstr 3556) 2016.
24. Satake H, Kato T, Oba K, Kotaka M, Kagawa Y, Yasui H, et al. Phase Ib/II Study of Biweekly TAS-102 in Combination with Bevacizumab for Patients with Metastatic Colorectal Cancer Refractory to Standard Therapies (BiTS Study). Oncologist. 2020;25(12):e1855-e63. Epub 2020/07/16. doi: 10.1634/theoncologist.2020-0643. PubMed PMID: 32666647.
25. Varghese AM, Cardin DB, Hersch J, Benson AB, Hochster HS, Makris L, et al. Phase I Study of Trifluridine/Tipiracil Plus Irinotecan and Bevacizumab in Advanced Gastrointestinal Tumors. Clin Cancer Res. 2020;26(7):1555-62. Epub 2020/01/12. doi: 10.1158/1078-0432.CCR-19-2743. PubMed PMID: 31924737.
26. Muro K, Boku N, Shimada Y, Tsuji A, Sameshima S, Baba H, et al. Irinotecan plus S-1 (IRIS) versus fluorouracil and folinic acid plus irinotecan (FOLFIRI) as second-line chemotherapy for metastatic colorectal cancer: a randomised phase 2/3 non-inferiority study (FIRIS study). Lancet Oncol. 2010;11(9):853-60. Epub 2010/08/17. doi: 10.1016/S1470-2045(10)70181-9. PubMed PMID: 20708966.
27. Kawakami T, Machida N, Yasui H, Kawahira M, Kawai S, Kito Y, et al. Efficacy and safety of irinotecan monotherapy as third-line treatment for advanced gastric cancer. Cancer Chemother Pharmacol. 2016;78(4):809-14. Epub 2016/08/28. doi: 10.1007/s00280-016-3138-z. PubMed PMID: 27566700.

28. Bang YJ, Ruiz EY, Van Cutsem E, Lee KW, Wyrwicz L, Schenker M, et al. Phase III, randomised trial of avelumab versus physician's choice of chemotherapy as third-line treatment of patients with advanced gastric or gastro-oesophageal junction cancer: primary analysis of JAVELIN Gastric 300. Ann Oncol. 2018;29(10):2052-60. Epub 2018/07/28. doi: 10.1093/annonc/mdy264. PubMed PMID: 30052729; PubMed Central PMCID: PMCPMC6225815.

Tables

Table 1. Patient characteristics

	Level 1A (N = 2) N (%)	Level 1B (N = 3) N (%)	Level 2B (N = 6) N (%)	Total (N = 11) N (%)
Median age (range), years	73 (58-76)	69 (66-76)	73 (61-78)	73 (58-78)
Gender				
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 3+ or in situ hybridization positive

Table2. 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 (%)	N (%)	N (%)	N (%)
Hematological toxicities						
Neutropenia	2 (100.0)	2 (100.0)	3 (100.0)	2 (66.7)	6 (100.0)	6 (100.0)
White blood cell count decreased	2 (100.0)	1 (50.0)	3 (100.0)	1 (33.3)	5 (83.3)	4 (66.7)
Anemia	2 (100.0)	2 (100.0)	2 (66.7)	1 (33.3)	3 (50.0)	2 (33.3)
Platelet count decreased	0 (0)	0 (0)	1 (33.3)	0 (0)	4 (66.7)	1 (16.7)
Lymphocyte count decreased	1 (50.0)	1 (50.0)	0 (0)	0 (0)	2 (33.3)	1 (16.7)
Febrile neutropenia	1 (50.0)	1 (50.0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)
Non-hematological toxicities						
Appetite loss	1 (50.0)	0 (0)	2 (66.7)	0 (0)	5 (83.3)	0 (0)
Diarrhea	1 (50.0)	0 (0)	2 (66.7)	0 (0)	2 (33.3)	0 (0)
Constipation	1 (50.0)	0 (0)	0 (0)	0 (0)	3 (50.0)	0 (0)
Fatigue	0 (0)	0 (0)	3 (100.0)	0 (0)	1 (16.7)	0 (0)
Mucositis	0 (0)	0 (0)	1 (33.3)	0 (0)	2 (33.3)	1 (16.7)
Gum infection	1 (50.0)	1 (50.0)	0 (0)	0 (0)	0 (0)	0 (0)
Peritoneal infection	0 (0)	0 (0)	1 (33.3)	1 (33.3)	0 (0)	0 (0)
γ-glutamyl transpeptidase increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)
Blood bilirubin increased	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (16.7)

Table3. Efficacy summary

	Level 1A (N = 2) N (%)	Level 1B (N = 3) N (%)	Level 2B (N = 6) N (%)	Total (N = 11) N (%)
CR	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) (%) [95% CI]	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) (%) [95% CI]	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

Figures

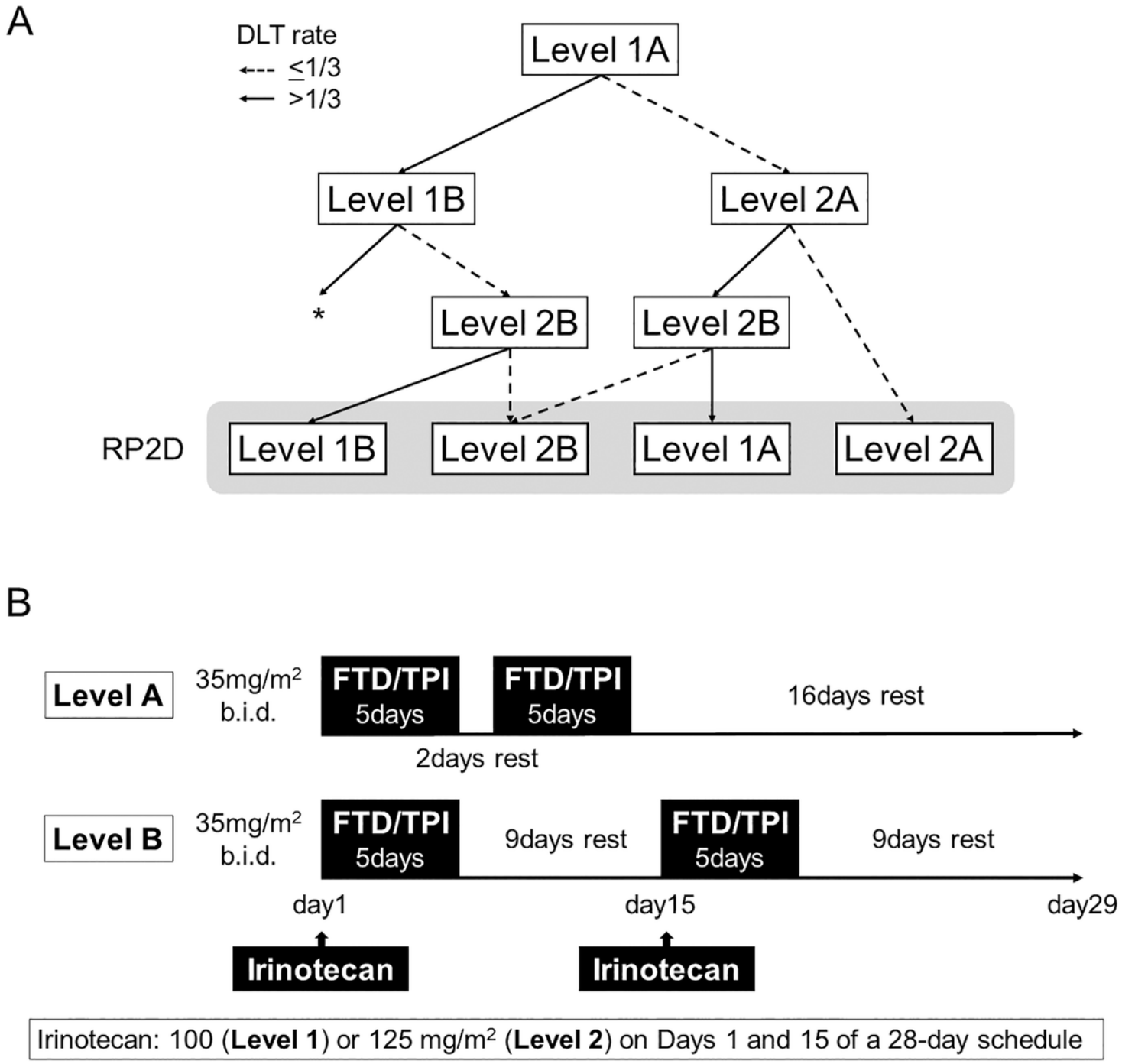

Figure 1

Study design and treatment. A. Dose level modification based on toxicity. Dose level modification will be based on observed toxicity from at least three subjects in the same cohort who have received investigational therapy according to the designated schedule for 28 days. *RP2D was finally judged by the investigators and the IDMC. B. Treatments. Patients were enrolled into four cohorts (Level 1A/1B/2A/2B) used an escalated dose of irinotecan [100 (Level 1) or 125 mg/m2 (Level 2) on days 1 and

15] with 2 schedules of 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.

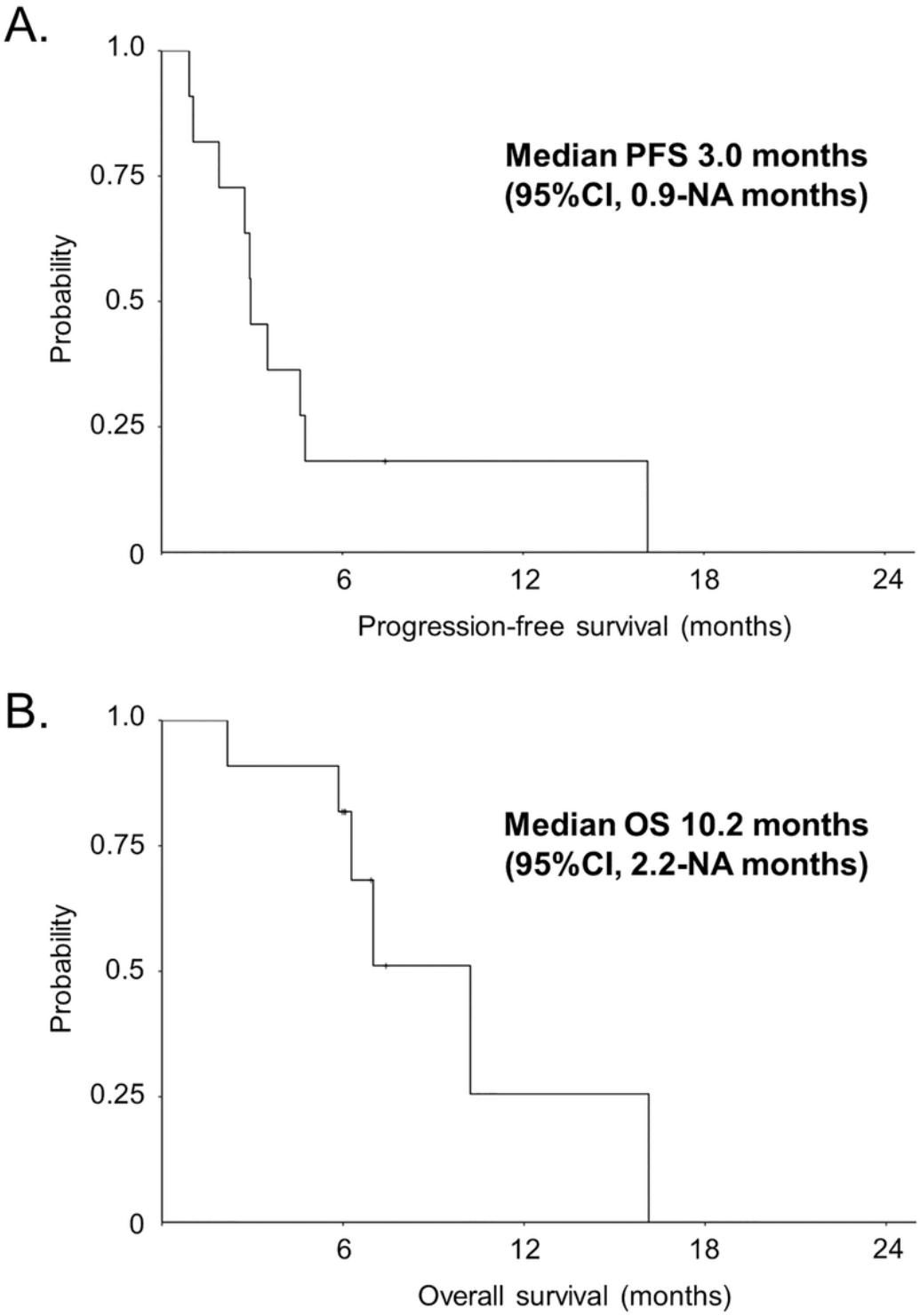

Figure 2

Kaplan-Meier plots of PFS and OS in all patients. A. The median PFS was 3.0 months (95% confidence interval [CI], 0.9- NA months). B. The median OS was 10.2 months (95%CI, 2.2- NA months).