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ORIGINAL ARTICLE

A phase II study of intrapatient dose escalation of biweekly trifluridine/tipiracil plus bevacizumab for colorectal cancer (E-BiTS study)☆

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Background: Trifluridine/tipiracil (FTD/TPI) plus bevacizumab (BEV) remains a standard of care for refractory metastatic colorectal cancer (mCRC), though hematological toxicities remain a concern. Although a biweekly regimen has shown favorable tolerability, the optimal biweekly dosage has yet to be established. Thus, this study was conducted to evaluate the feasibility and clinical impact of intrapatient dose escalation of biweekly FTD/TPI plus BEV.

Materials and methods: This multicenter, single-arm phase II trial included patients with refractory mCRC who had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-1. Eligible patients received biweekly FTD/TPI (35 mg/m^2 twice daily on days 1-5, every 2 weeks) and BEV (5 mg/kg on day 1). The FTD/TPI dose could be escalated up to 30 mg/day based on tolerability during cycles 2-4. The primary endpoint was disease control rate, whereas the secondary endpoints included progression-free survival (PFS), overall survival (OS), relative dose intensity, and safety.

Results: Among the 36 enrolled patients, 34 were included in the full analysis set. The median age was 65 years (range 39-79 years); 76% had ECOG PS 0, 56% had RAS mutations, and 79% had two or more metastatic organs. Dose escalation was feasible in 91% of the patients. The disease control rate was 72.7% (80% confidence interval 60.4% to 82.8%), median PFS was 5.6 months, and median OS was 17.6 months, with a median follow-up duration of 18.0 months. Patients who experienced grade $\geq$2 neutropenia had significantly improved outcomes (PFS, 7.0 versus 2.3 months; OS, not reached versus 10.6 months). Hematologic toxicities were manageable, with no febrile neutropenia and only three treatment-related serious adverse events.

Conclusions: Intrapatient dose escalation of biweekly FTD/TPI plus BEV was feasible and well tolerated and may enhance the efficacy of refractory mCRC treatment. Nonetheless, further studies are warranted to validate this individualized dosing strategy.

Key words: colorectal cancer, biweekly trifluridine/tipiracil plus bevacizumab, intrapatient dose escalation strategy

INTRODUCTION

Trifluridine/tipiracil (FTD/TPI), an oral anticancer agent, has been a standard treatment option for patients with refractory metastatic colorectal cancer (mCRC) in later-line settings.[1] Recently, the international phase III SUNLIGHT trial demonstrated that the addition of bevacizumab (BEV) to FTD/TPI significantly improved overall survival (OS) rates compared with FTD/TPI monotherapy,[2] establishing this combination as the new global standard of care. Incidence rates of hematological toxicities, such as neutropenia, however, have been relatively high, often inducing treatment delays and dose reductions in clinical practice. Moreover, the standard FTD/TPI regimen (administered orally twice daily on days 1-5 and 8-12 of a 28-day cycle) is complex and has been associated with a higher risk of dosing errors.

A simplified biweekly regimen of FTD/TPI (administered twice daily on days 1-5 every 2 weeks) in combination with BEV, however, has recently been developed as an alternative

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to the standard regimen. This modified regimen has been evaluated in three independent phase II trials, all of which reported a lower incidence of grade ≥3 neutropenia while maintaining compatible antitumor effects.[3-5] These findings suggest the potential clinical advantages of this modified regimen in terms of safety and ease of administration. Given the lack of dose-finding studies or pharmacokinetic evaluations, however, the optimal dosing and dose intensity of a biweekly FTD/TPI regimen has yet to be fully established.

A subgroup analysis of the RECOURSE study indicated that chemotherapy-induced neutropenia (CIN) during standard FTD/TPI monotherapy was associated with improved OS and progression-free survival (PFS). In the mentioned analysis, plasma concentrations of FTD above the median area under the curve (AUC) were correlated with both a higher incidence of neutropenia and longer survival outcomes.[6] Notably, patients who did not develop neutropenia exhibited no survival benefits, suggesting that the occurrence of neutropenia may serve as a surrogate marker for treatment efficacy. Several papers have also reported that CIN might be an indicator of outcomes in mCRC patients receiving FTD/TPI plus BEV.[7,8]

Based on these findings, we hypothesized that some patients receiving biweekly FTD/TPI plus BEV might not achieve adequate FTD concentrations considering the low incidence of neutropenia.[3-5] Therefore, we designed a treatment strategy involving interpatient dose escalation of this regimen with the aim of improving antitumor activity and evaluating tolerability with respect to adverse events (AEs). Accordingly, we conducted the E-BiTS study in patients with refractory mCRC.

MATERIALS AND METHODS

Patients and study design

The E-BiTS study was an open-label, single-arm, multicenter phase II trial that enrolled patients aged ≥20 years with advanced or unresectable mCRC. The eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; presence of measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.1; and refractory or intolerance to fluoropyrimidine, oxaliplatin, irinotecan, angiogenesis inhibitors, and anti-epidermal growth factor receptor (anti-EGFR) antibodies in the case of *RAS* wild-type mCRC. Additional inclusion criteria included no prior exposure to FTD/TPI, the ability to take oral medication, and adequate organ function. Specific renal function requirements included a serum creatinine ≤1.5 mg/dl and creatinine clearance ≥60 ml/min (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105571). Key exclusion criteria included concurrent malignancies requiring chemotherapy and active infections requiring systemic treatment (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Table 1. Patient characteristics

Characteristics (n = 34)	n (%)
Age, years (range)	65 (39-79)
Sex	
Female/male	17 (50)/17 (50)
ECOG PS	
0/1	26 (76)/8 (24)
Primary site	
Colon/rectum	26 (76)/8 (24)
Right-/left-sided	6 (18)/28 (82)
Histological grade	
Well, moderately, poorly, mucinous, or signet	34 (100)/0
Number of metastatic organs	
1/≥2	7 (21)/27 (79)
Metastatic organ	
Liver	23 (68)
Lung	26 (76)
Lymph node	13 (38)
Peritoneum	8 (24)
RAS status	
Wild-type/mutant	15 (44)/19 (56)
BRAF status	
Wild-type/mutant	33 (97)/1 (3)
MSI status	
MSS/MSI-H/unknown	33 (97)/0/1 (3)
HER2 status	
−/+/unknown	16 (47)/2 (6)/16 (47)
Previous lines of therapy	
1	3 (9)
2	16 (47)
3	9 (26)
≥4	6 (18)
Previous therapy	
Fluoropyrimidine	34 (100)
Oxaliplatin	34 (100)
Irinotecan	34 (100)
Anti-VEGF monoclonal antibody	34 (100)
The anti-EGFR monoclonal antibody	15 (44)
Primary tumor resection	
Yes/no	22 (65)/12 (35)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI-H, microsatellite instability high; MSS, microsatellite stability; VEGF, vascular endothelial growth factor.

Treatment and dose-escalation criteria for FTD/TPI

Patients received biweekly FTD/TPI (35 mg/m^2 twice daily on days 1-5, every 2 weeks) plus BEV (5 mg/kg on day 1, every 2 weeks) until disease progression or intolerable toxicity. The treatment protocol could be initiated when all initiation criteria were met in each cycle (Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.105571). Based on the predefined dose-escalation criteria (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2025.105571), the daily dose of FTD/TPI could be escalated by 10 mg/day per cycle, up to a maximum of 30 mg/day (dose levels 0-3), during cycles 2 through 4 (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2025.105571). This period was defined as the dose-escalation phase. Dose reduction was mandated when any of the dose reduction criteria were met (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2025.105571). The treatment protocol was discontinued when patients met any of the discontinuation criteria (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Endpoints and statistical analysis

The primary endpoint was disease control rate (DCR), defined as the proportion of patients achieving a complete response,

partial response, or stable disease based on computed tomography (CT) conducted every 8 weeks. Considering that the DCR of biweekly FTD/TPI plus BEV was 59.1% in the previous BiTS study,[3] we set the threshold and expected DCR at 60% and 80%, respectively. A total of 36 patients were required to test this hypothesis with 80% power and a one-sided α of 0.10, allowing for a 20% dropout rate.

The secondary endpoints included OS, PFS, response rate (RR), relative dose intensity (RDI) of FTD/TPI, rate of FTD/TPI dose escalation, and AEs. Efficacy was primarily assessed in the per-protocol set (PPS), which included all registered patients excluding those deemed ineligible after enrollment, those in whom efficacy could not be evaluated due to insufficient follow-up, and those with major protocol deviations related to dosing, treatment schedule, or concomitant therapy. Safety was evaluated in the safety population, defined as all patients who received at least one dose of FTD/TPI. Other endpoints were evaluated in the full analysis set (FAS), which included all registered patients excluding those deemed ineligible after enrollment. OS was defined as the period from registration to death from any cause, with censoring on the last day the patient had been confirmed to be alive. PFS was defined as the period from registration to disease progression or death, whichever occurred first, with censoring on the last day the patient had been confirmed to be alive without progression. Median OS and PFS were estimated using the Kaplan–Meier method. RDI of FTD/TPI was calculated using the following formula:

$$\text{RDI of FTD}\Big/\text{TPI} = \frac{\text{Actual administered DI of FTD}/\text{TPI}}{\text{Planned administered DI of FTD}/\text{TPI}}.$$

The actual administered DI of FTD/TPI was calculated using the following formula:

$$\text{Actual administered DI of FTD}\Big/\text{TPI}\,(\text{mg}/\text{week}) = \frac{\text{Actual administration amount of FTD}/\text{TPI}\,(\text{mg})}{2\text{ weeks}}.$$

The planned administered DI of FTD/TPI was calculated using the following formula:

$$\text{Planned administered DI of FTD}\Big/\text{TPI}\,(\text{mg}/\text{week}) = \frac{\text{Planned administration amount of FTD}/\text{TPI at first cycle}\,(\text{mg})}{2\text{ weeks}}.$$

Confidence intervals (CIs) for proportions were calculated using the Clopper–Pearson exact method based on the binomial distribution. AEs were graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Subgroup analyses of clinical outcomes, including DCR, OS, and PFS, were conducted according to neutropenia grade observed during all treatment cycles and specifically during cycles 1-2. *P* values for each comparison were calculated using Fisher's exact test. Subgroup analyses of OS and PFS based on the maximum dose level achieved, as well as groupings according to dose level (0, 1, or $\geq$2) during cycles 1-4, were also carried out. Univariate analyses were conducted using the Cox proportional hazards model, from which hazard ratios (HRs), 95% CI, and corresponding *P* values were calculated. Additionally, we explored patient characteristics associated with the likelihood of FTD/TPI dose escalation.

Ethics and dissemination

This study was conducted in compliance with the Clinical Trials Act in Japan and the Declaration of Helsinki and was approved by the Certified Review Board of Aichi Cancer Center Hospital (CRB4200002). Written informed consent was obtained from all participants before enrollment. This trial has been registered with the Japan Registry of Clinical Trials (clinical trial identifier: jRCTs041220085).

RESULTS

Patient characteristics

Between 1 November 2022 and 28 December 2023, a total of 36 patients were enrolled from seven participating institutions. Among them, 2 patients were excluded from the FAS for not meeting the inclusion criterion on renal function, resulting in 34 patients being included in the FAS. Among these patients, 1 was transferred to another hospital before undergoing the first protocol-mandated CT evaluation and was therefore excluded from the PPS, which comprised 33 patients (Figure 1).

The baseline characteristics of the FAS population are summarized in Table 1. The median age was 65 years (range 39-79 years), and the majority of the patients (76%) had an ECOG PS of 0. Most patients (82%) had left-sided primary tumors, and 56% harbored RAS mutations. Additionally, 91% of the patients received two or more previous lines of chemotherapy, whereas 79% had two or more metastatic organs, indicating a relatively high disease burden (Table 1).

Dose escalation of FTD/TPI

Among the patients in the FAS population, 91% were able to escalate their FTD/TPI dose by at least one level during

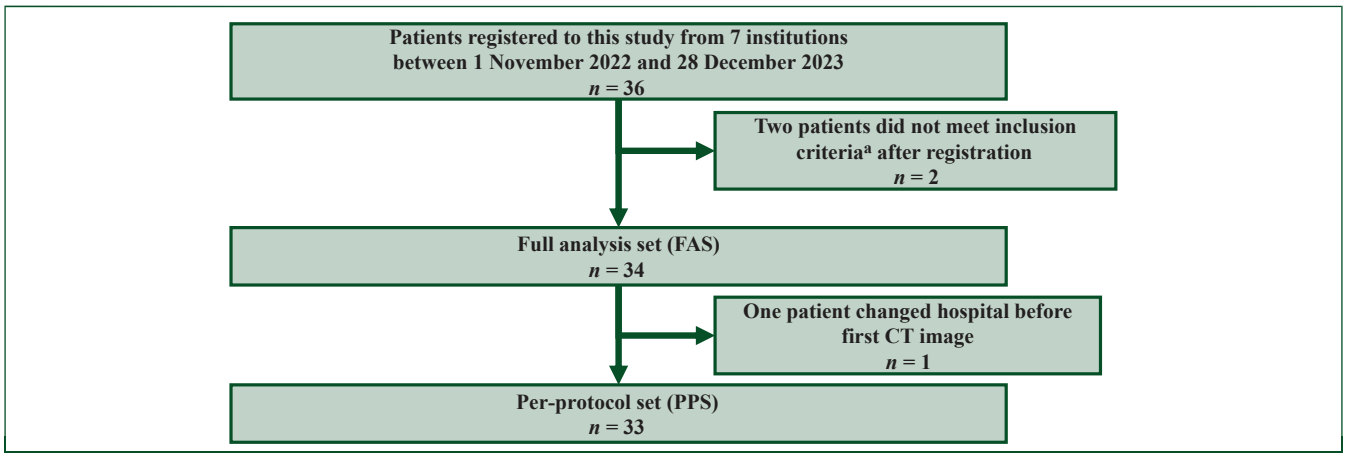


Figure 1. Patient flow.
CCr, creatinine clearance; CT, computed tomography.
[a]Both patients did not meet criteria of CCr.

the dose-escalation phase, whereas the remaining 9% were unable to do the same (Figure 2). The FTD/TPI dose was reduced in two patients (5.9%) due to grade 1 anorexia and grade 2 fatigue. The most common reason for failure of dose escalation was neutropenia (42.5%) at all timings in which the planned dose escalation was not possible (Supplementary Table S6, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Dose intensity of FTD/TPI

Both the mean and median RDI of FTD/TPI increased from one cycle to another during the dose-escalation phase. The mean/median of RDI during the dose-escalation phase and during the whole treatment protocol was 107.1%/108.3% and 110.6%/110.0% in the FAS population, respectively (Supplementary Table S7, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Efficacy

The DCR was 72.7% (80% CI 60.4% to 82.8%), whereas the ORR was 9.1% (Figure 3). Median PFS was 5.6 months (95% CI 2.7-6.5 months), whereas the median OS was 17.6 months (95% CI 10.1 months-not available), with a median follow-up of 18.0 months at the final analysis on 10 May 2024 (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2025.105571). DCR, PFS, and OS were significantly increased in patients who experienced grade $\geq$2 neutropenia during protocol treatment (DCR: 89% versus 50%, $P = 0.02$; PFS: 7.0 versus 2.3 months, HR 0.24, 95% CI 0.11-0.55, $P < 0.001$; OS: not reached versus 10.6 months, HR 0.37, 95% CI 0.14-0.97, $P = 0.04$) (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2025.105571). Similarly, patients who experienced grade $\geq$2 neutropenia during cycles 1-2 had a higher DCR than those who did not (100% versus 63%,

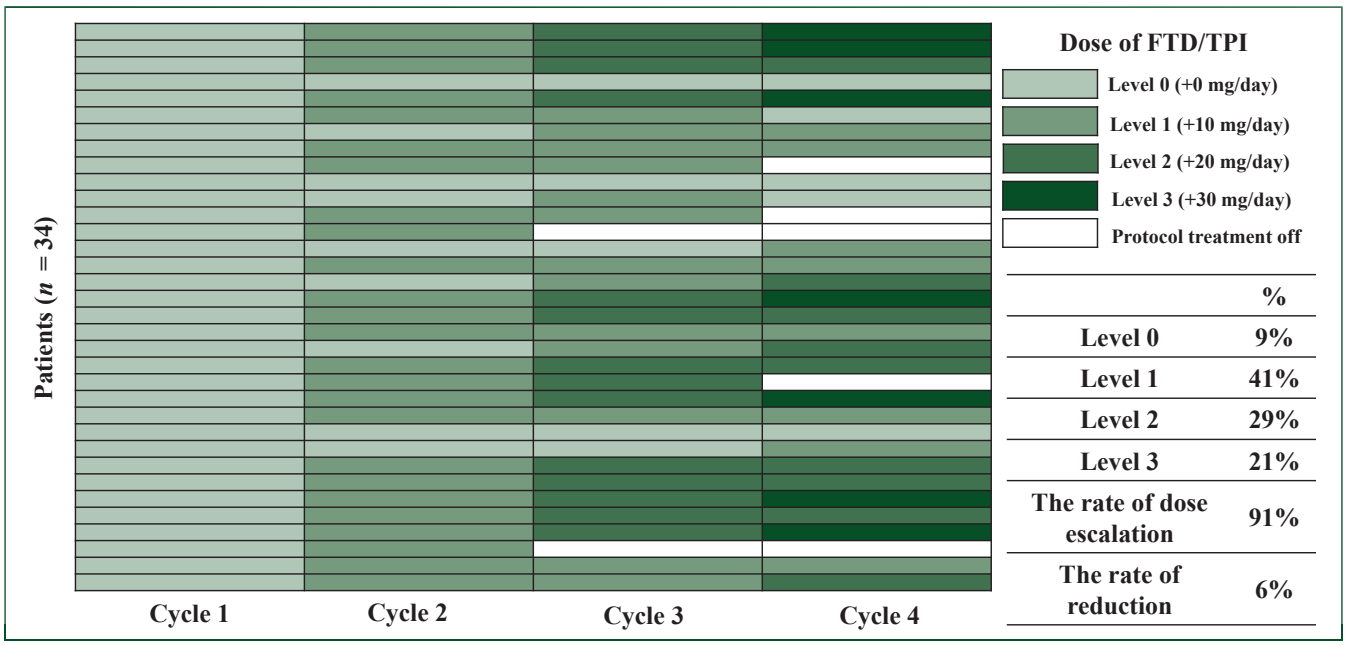


Figure 2. Status of FTD/TPI dose during the dose-escalation phase.
FTD/TPI, trifluridine/tipiracil.

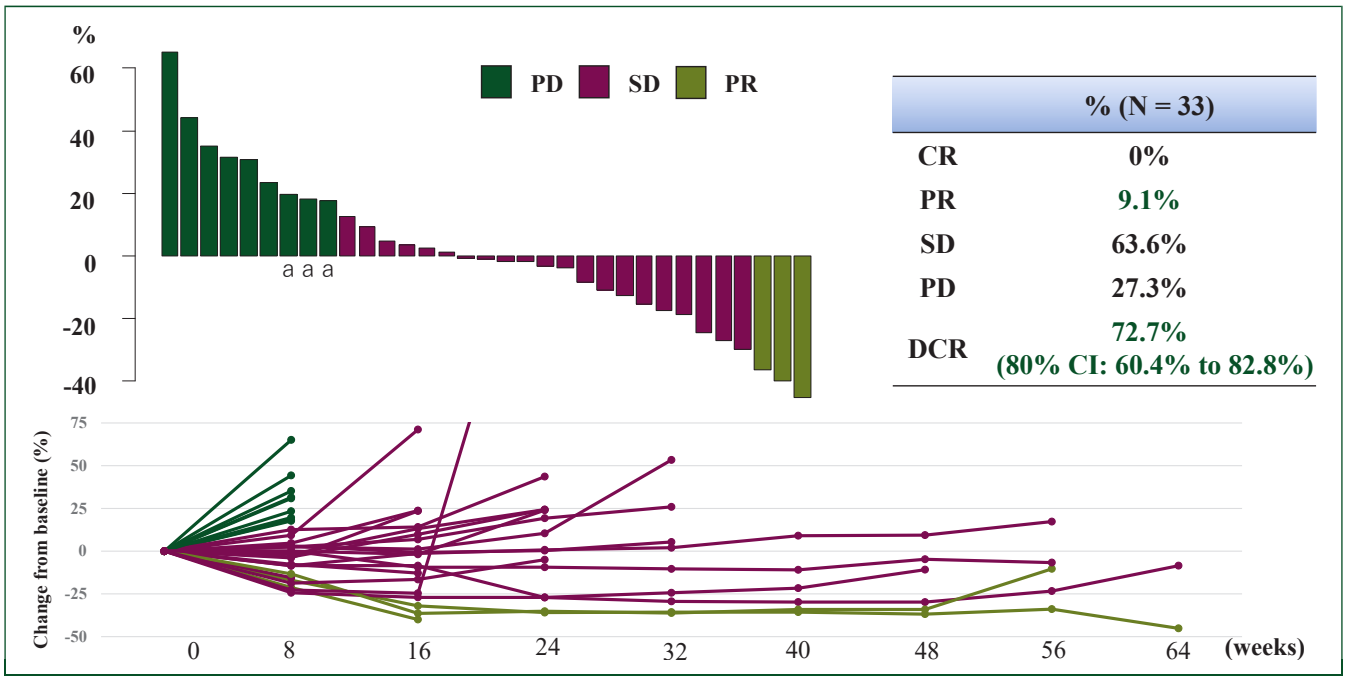


Figure 3. Best tumor response.
CI, confidence interval; CR, complete response; CT, computed tomography; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]New lesion was detected at initial CT.

$P = 0.04$), although no statistically significant differences in PFS and OS were observed (PFS: 6.0 versus 3.9 months, HR 0.58, 95% CI 0.25-1.36, $P = 0.21$; OS: not reached versus 13.2 months, HR 0.71, 95% CI 0.23-2.18, $P = 0.55$) (Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2025.105571). OS was also significantly improved in patients who received two or more dose levels during cycles 1-4 (not reached versus 9.8 months, HR 0.27, 95% CI 0.09-0.77, $P = 0.014$), although no significant difference in PFS was observed (6.0 months versus 4.5 months, HR 0.72, 95% CI 0.35-1.50, $P = 0.38$) (Supplementary Figure S5, available at https://doi.org/10.1016/j.esmoop.2025.105571). No specific patient characteristics were found to be associated with successful dose escalation (Supplementary Table S8, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Subsequent therapy

A total of 24 patients (70.6%) received subsequent therapy, with regorafenib being the most frequently prescribed agent (38.2%). At the final analysis, four patients remained on treatment, whereas six patients received no subsequent therapy (Supplementary Table S9, available at https://doi.org/10.1016/j.esmoop.2025.105571).

Safety

The incidence of any-grade and grade ≥3 neutropenia was 74% and 24%, respectively. During the dose-escalation phase, any-grade and grade ≥3 neutropenia were observed in 61% (19/31) and 0% of those in whom the FTD/TPI dose could be escalated, respectively. There were no patients who discontinued treatment protocol due to AEs during the dose-escalation phase. The incidence of grade ≥3 anemia was 21%. Grade ≥3 hypertension and proteinuria, which have been considered BEV-related AEs, were observed in 9% and 6% of patients, respectively. None of the patients developed febrile neutropenia. Three treatment-related serious AEs (i.e. one colonic perforation, one kidney infection, and one upper gastrointestinal hemorrhage) were observed. No treatment-related deaths occurred (Table 2), and no relationship between the FTD/TPI dose and neutropenia grade was observed (Supplementary Table S10, available at https://doi.org/10.1016/j.esmoop.2025.105571).

DISCUSSION

The current phase II study (E-BiTS) demonstrated that an intrapatient dose-escalation strategy using a biweekly FTD/TPI plus BEV regimen was feasible and tolerable while having promising clinical activity in patients with mCRC. Notably, our study was able to achieve its primary endpoint, with a DCR of 72.7%, an ORR of 9.1%, and a reported median PFS and OS of 5.6 and 17.6 months, respectively, which appear to be better than previously reported results using fixed-dose biweekly schedules.

Despite the established efficacy of the standard FTD/TPI (days 1-5 and 8-12 in a 28-day cycle) plus BEV regimen in mCRC, its use is often limited by dosing complexity and frequent hematologic toxicities, particularly neutropenia.[2] Previous phase II and III trials have reported incidences of grade ≥3 neutropenia ranging from 43.1% to 72%.[2,9-11] Hence, biweekly regimens had been developed to improve convenience and reduce toxicity.[3-5] Moreover, a randomized phase III trial comparing biweekly and conventional FTD/TPI plus BEV for mCRC (i.e. the PRABITAS study) is

Table 2. Adverse events

Adverse events ($n = 34$)	n (%)					
	Any grade	Grade ≥3	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	23 (68)	6 (18)	4 (12)	13 (38)	5 (15)	1 (3)
Neutropenia	25 (74)	8 (24)	6 (18)	11 (32)	7 (21)	1 (3)
Anemia	26 (76)	7 (21)	8 (24)	11 (32)	6 (18)	1 (3)
Thrombocytopenia	10 (29)	0	7 (21)	3 (9)	0	0
AST, increased	7 (21)	0	7 (21)	0	0	0
ALT, increased	6 (18)	0	6 (18)	0	0	0
Blood bilirubin increased	5 (15)	0	4 (12)	1 (3)	0	0
Nausea	13 (38)	0	6 (18)	7 (21)	0	0
Vomiting	10 (29)	0	8 (24)	2 (6)	0	0
Diarrhea	13 (38)	0	10 (29)	3 (9)	0	0
Mucositis	8 (24)	0	5 (15)	3 (9)	0	0
Fatigue	20 (59)	0	12 (35)	8 (24)	0	0
Anorexia	22 (65)	1 (3)	15 (44)	6 (18)	1 (3)	0
Alopecia	4 (12)	0	1 (3)	3 (9)	0	0
Infection	5 (15)	1 (3)	0	4 (12)	1 (3)	0
Febrile neutropenia	0	0			0	0
Hypertension	17 (50)	3 (9)	4 (12)	10 (29)	3 (9)	0
Proteinuria	13 (38)	2 (6)	4 (12)	7 (21)	2 (6)	0
Hemorrhage	8 (24)	1 (3)	5 (15)	2 (6)	1 (3)	0
Thromboembolic events	0	0	0	0	0	0
Intestinal perforation	1 (3)	1 (3)	0	0	1 (3)	0
Treatment-related serious adverse events	$n = 3$[a]					
Treatment-related death	$n = 0$					

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a]One colonic perforation, one kidney infection, and one upper gastrointestinal hemorrhage.

currently ongoing.[12] Prior trials have suggested, however, that lower incidence rates of neutropenia (15.9%-24%) may reflect underexposure to FTD, potentially compromising efficacy.[3-5]

Although several dose-finding phase I studies of FTD/TPI using a conventional 3 + 3 dose-escalation design have been conducted,[13-16] the possibility of FTD/TPI dose escalation beyond 70 mg/m^2/day has remained underexplored. Subgroup analysis of the RECOURSE study showed similar rates of grade ≥3 neutropenia regardless of race.[17] The FTD/TPI dose in a biweekly regimen was determined to be 35 mg/m^2 twice daily, which was the same as the conventional FTD/TPI dosage according to the rolling six design, dose-finding de-escalation method, in the BiTS study.[3] In this context, the E-BiTS study sought to individualize dosing by allowing intrapatient escalation based on tolerability in the hope of potentially optimizing therapeutic intensity while maintaining safety.

Notably, the efficacy of FTD, which exerts its cytotoxic activity primarily through DNA incorporation, is exposure-dependent, with the AUC being a key determinant of its antitumor effects. In fact, the RECOURSE trial found that a higher FTD AUC correlated with both increased incidence of neutropenia and improved survival, suggesting that neutropenia may serve as a clinically accessible pharmacodynamic marker.[6] This relationship supports the concept that fixed dosing may promote underexposure in certain patients, particularly those with higher drug clearance or altered metabolism. Intrapatient dose escalation enables dynamic adjustment of drug intensity, which could potentially improve efficacy while maintaining tolerability.

The antitumor effects, including DCR, RR, PFS, and OS, observed in the present study were relatively better than those reported in previous studies.[3-5] The RDI of FTD/TPI was well maintained after five cycles. Although the present study failed to identify specific characteristics associated with dose escalation, escalating the FTD/TPI dose might induce good clinical outcomes. Hence, achieving adequate concentrations of FTD, which could lead to neutropenia, might have promoted better clinical outcomes in patients who were able to escalate the FTD/TPI dose.

The high feasibility rate of dose escalation (91%), the high mean/median RDI of FTD/TPI during the whole treatment protocol (110.6%/110.0%), and the lack of a correlation between dose level and neutropenia severity support the notion that fixed dosing may cause subtherapeutic exposure in a subset of patients. The present findings align with previous reports that CIN may reflect adequate systemic exposure and act as a positive prognostic factor. Indeed, studies have shown that CIN was associated with improved survival not only in patients treated with FTD/TPI,[18-20] but also across various cytotoxic regimens and ethnic populations,[21,22] underscoring its generalizable role as a surrogate efficacy marker.

Importantly, all hematological toxicities observed in this study remained manageable, with no cases of febrile neutropenia and only three treatment-related serious AEs. The incidence and nature of these AEs were consistent with those reported in previous studies.[3-5] Notably, the absence of a clear dose-toxicity relationship suggests that tailored dose escalation can be safely implemented in selected patients. Nonetheless, patients who were unable to escalate

their FTD/TPI dose could have possibly already achieved sufficient systemic exposure at the initial dose, whereas others may have required higher dosing to reach optimal FTD concentrations. This approach may be especially beneficial for patients with a preserved performance status and adequate renal function who can tolerate higher dose intensity. Conversely, patients with renal impairment or frailty may still require careful dose limitation. Hence, future studies should consider integrating pharmacokinetic monitoring or early-onset CIN as biomarkers for dose adjustment which could further individualize FTD/TPI therapy.

Nevertheless, several limitations of the current study must be acknowledged. Firstly, this study enrolled a relatively fit population, with 76% having an ECOG PS of 0, which was higher than that reported in previous pivotal phase III trials (48%-55%).[1,2] Secondly, TPI is an inhibitor of thymidine phosphorylase, the enzyme that degrades FTD, and is excreted renally. Therefore, stringent renal function criteria were included, potentially excluding patients at risk of FTD overexposure. Thirdly, this study did not collect pharmacokinetic and pharmacodynamic data, precluding a direct assessment of drug exposure and its correlation with efficacy or toxicity. Finally, the single-arm design and limited sample size restricted the establishment of definitive conclusions.

In conclusion, the E-BiTS study highlights the feasibility and potential clinical utility of an intrapatient dose-escalation strategy of biweekly FTD/TPI plus BEV in refractory mCRC. This individualized dosing approach may improve the efficacy of FTD/TPI plus BEV through optimized systemic exposure without increasing toxicity. These findings merit validation in larger controlled studies and support future efforts toward precision dosing in chemotherapy.

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DISCLOSURE

MW reports receiving honoraria from Daiichi-Sankyo Co., Ltd. and Ono Pharmaceutical Co., Ltd. HTan reports receiving honoraria from Ono Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd., Eli Lilly Japan K.K., Chugai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., and a research grant from Takeda Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., and Ono Pharmaceutical Co., Ltd. AM reports receiving honoraria from Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol Myers Squibb Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K. YS reports receiving honoraria from Eli Lilly Japan K.K., Bristol Myers Squibb Co., Ltd., Guardant Health, Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co. Ltd., Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Merck Biopharma Co., Ltd, Bayer, Merck Sharp & Dohme (MSD) Co., Ltd., AstraZeneca K.K., Astellas Pharma Inc., Sysmex, and received a research grant from Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co. Ltd., Parexel International Inc, Ono Pharmaceutical Co., Ltd., CMIC Shift Zero K.K., PRA Health Sciences, Inc., Amgen Co., Ltd., Bristol Myers Squibb Co., Ltd., Astellas Pharma Inc., DNA Chip Research Inc., IQVIA Services Japan K.K., ICON Clinical Research, Takeda Pharmaceutical Co., Ltd., and consulting or advisory role in Merck Biopharma Co., Ltd., Daiichi-Sankyo Co., Ltd., and Guardant Health. HTak reports receiving honoraria from Bristol Myers Squibb Co., Ltd., Guardant Health Japan. CI reports receiving honoraria from Astellas Pharma Inc., Chugai Pharmaceutical Co., Ltd., MSD K.K., Ono Pharmaceutical Co., Ltd., holds stocks/shares of Daiichi-Sankyo Co., Ltd., Eisai Co., Ltd, and received a research grant from Astellas Pharma Inc., Eisai Co., Ltd, Ono Pharmaceutical Co., Ltd. SM reports receiving honoraria from MSD K.K., Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., Ltd., Taiho Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. and received a research grant from Caris Life Science. TK reports receiving honoraria from MSD Co., Ltd., Daiichi-Sankyo Co., Ltd., Ono Pharmaceutical Co., Ltd, Taiho Pharmaceutical Co., Ltd., Bristol Myers Squibb K.K., and Merck Biopharma Co., Ltd. and a research grant from Astellas Pharma Inc., AstraZeneca K.K., Amgen Inc., Daiichi-Sankyo Co., Ltd., Incyte Biosciences Japan G.K., MSD Co., Ltd., Novartis Pharma K.K., Ono Pharmaceutical Co., Ltd., Pfizer Inc. SY reports receiving honoraria from Eli Lilly Japan K.K., Chugai Pharmaceutical Co., Ltd., Taiho Pharmaceutical Co., Ltd., Bristol Myers Squibb K.K., Ono Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., MSD K.K., Bayer Yakuhin Ltd., Merck Biopharma Co., Ltd., Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Roche Diagnostics K.K., Nippon Boehringer Ingelheim Co., Ltd., and Miyarisan Pharmaceutical Co., Ltd. KM reports receiving honoraria from Eli Lilly Japan K.K, Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and received statistical consultancy from Daiichi Sankyo Co., Ltd. KM reports receiving honoraria from MSD Co., Ltd., Bristol Myers Squibb Co., Ltd., Ono Pharmaceutical Co., Ltd., Eli Lilly Co., Ltd., Takeda Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Taiho Pharmaceutical Co., Ltd., and research funding from Astellas Pharmaceutical Co., Ltd., Amgen Co., Ltd., Sanofi Co., Ltd., Novartis Co., Ltd., Parexel International, PRA Health Sciences, Taiho Pharmaceutical Co., Ltd., MSD Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., and consulting or advisory role in Amgen Co., Ltd., Astellas Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., AstraZeneca Co., Ltd., Chugai Pharmaceutical Co., Ltd., and plays advisory role in Astellas Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Amgen Co., Ltd., and AstraZeneca Co., Ltd. All other authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and/or analyzed during the present study are not available from the corresponding author.

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