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Phase II study of DFP-10917, a deoxycytidine analog, given by 14-day continuous intravenous infusion for chemotherapy-refractory advanced colorectal cancer

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Abstract

Background: DFP-10917 is a cytotoxic deoxycytidine analogue that causes DNA fragmentation, G₂/M-phase arrest, and apoptosis. This agent has been shown to have antitumor activity against colorectal cancer (CRC) in preclinical studies and to be tolerable in patients. The purpose of our phase II trial was to evaluate the safety, efficacy and pharmacogenomics of DFP-10917 as well as DNA damage studies in patients with advanced CRC refractory to cytotoxic chemotherapy.

Methods: In this single-arm, Simon two-stage, phase II trial, patients with chemotherapy-refractory advanced CRC received 2.0 mg/m²/day DFP-10917 via 14-day continuous infusion. Enrollment criteria included age ≥ 18 years, Eastern Cooperative Oncology Group status of 0 or 1, and adequate organ function. The primary endpoint was 3-month progression-free survival, defined as the proportion of patients who did not have progressive disease or death within 3 months of starting therapy. All patients who received any amount of DFP-10917 were included in the safety analysis. DNA damage study was assessed by comet assay.

Results: Of 28 patients initially enrolled, 26 received DFP-10917. Three patients (12%) were progression free at 3 months. The median progression-free survival was 1.3 months (95% confidence interval, 1.3–1.6 months). There were no complete or partial responses. Most patients (n=20, 77%) had progressive disease, and only six (23%) had stable disease at any time. The trial

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Compliance with Ethical Standards

Conflict of Interest

All authors declare no potential conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Written informed consent to participate in the study was obtained from each patient before study enrollment and the performance of any study-specific procedures.

was terminated according to the pre-planned stopping rule. The most frequent (5%) medication-related grade 3 or higher adverse events were neutropenia (n=10, 38%), fatigue (n=4, 15%), anemia (n=3, 12%), and leukopenia (n=3, 12%). DNA strand-breaks were detected after infusion (medians of % tail intensity were 2.89 and 12.64 on day 1 and day 15, respectively, $p<0.001$. sign test).

Conclusion: Overall, single-agent DFP-10917 did not show meaningful antitumor activity in chemotherapy-refractory advanced CRC. The safety profile of DFP-10917 was tolerable and similar to that observed in earlier clinical studies.

Keywords

DFP-10917; chemotherapy-refractory; colorectal cancer; phase II; pharmacogenomics

Introduction

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in the United States and accounts for approximately 8% of all cancer-related deaths. The number of new U.S. cases in 2016 is estimated to be 70,000, and about 20% of these cases will be metastatic at the time of presentation [1], Systemic therapies including cytotoxic agents (fluoropyrimidines, oxaliplatin, and irinotecan), monoclonal antibodies (cetuximab and panitumumab), and anti-vascular endothelial growth factor antibodies (bevacizumab) have improved survival in patients with unresectable CRC [2], However, there is no standard treatment for patients who are unable to tolerate these agents or who have refractory disease.

DFP-10917 is one agent being tested in this group of patients. DFP-10917 [4-amino-1-(2-cyano-2-deoxy- β -D-arabinofuranosyl)-2(IH)-pyrimidinone or CNDAC] is a nucleoside analogue similar to deoxycytidine [3, 4], Previous *in vitro* tumor models have demonstrated the cytotoxic effects of DFP-10917 (and its prodrug Sapacitabine also known as CYC682) against various cancer cell lines. Similar to the other deoxycytidine analogues (e.g. gemcitabine, and cytarabine), DFP-10917 which was formerly known as TAS-109 is activated by deoxycytidine kinase (DCK) and is inactivated by cytidine deaminase (CDA) [5]. High doses of DFP-10917 inactivate DNA polymerase and block DNA synthesis, leading to S-phase arrest. At low concentrations, DFP-10917 causes breakage of the DNA strand. DNA repair is then initiated by checkpoint regulators, which causes G₂/M-phase arrest and ultimately results in apoptosis. CNddC [4-amino-1-(2-cyano-2,3-didehydro-2,3-dideoxy- β -D-arabinofuranosyl)-2 (IH)-pyrimidinone] was detected in the nucleosides extracted from cells treated with DFP-10917 at a low concentration; this finding indicates DNA self-strand-breakage [6–8, 21] Thus, the mechanism of action of low-dose exposure to DFP-10917 appears to be fragmentation of DNA molecules.

Pre-clinical *in vivo* studies using mouse models of human colon adenocarcinoma have shown that prolonged exposure to DFP-10917 (14-day continuous infusion) at a low concentration provides greater antitumor activity and lower levels of toxicity than shorter durations of DFP-10917 exposure at higher concentrations. On the basis of these preclinical data, two phase I clinical trials were performed with 29 patients [9]. DFP-10917 was administered via continuous infusion for 14 days followed by a 7-day rest period (study 1)

or via continuous infusion for 7 days followed by a 7-day rest period (study 2). No partial or complete responses were seen. Of the 13 patients who received the 14-day infusion (median number of cycles, 2), five (38%) had stable disease as the best response (median time to disease progression, 53 days). Of the nine patients treated with the 7-day infusion (median number of cycles, 3), three (33%) had stable disease as their best response (median time to disease progression, 62 days). Overall, continuous infusion was feasible and well tolerated, and the predominant drug-related and severe toxicities were hematologic. The most frequent adverse events—and dose-limiting toxicities (DLT)—were neutropenia, anemia, febrile neutropenia, leukopenia, and thrombocytopenia. The maximum tolerated doses were 2.0 mg/m²/day for 14-day continuous infusion and 3.0 mg/m²/day for 7-day continuous infusion. However, a patient who was treated with the 3.0-mg/m²/day dose had a dose-limiting toxicity of grade 3 febrile neutropenia. Patients who received the 14-day continuous infusion at 2.0 mg/m²/day did not experience any dose-limiting toxicity. Therefore, 14-day continuous intravenous infusion at 2.0 mg/m²/day was recommended for further study in a phase II clinical trial.

On the basis of these preclinical and clinical data, we conducted a phase II, multicenter, open-label clinical trial to evaluate the safety and efficacy of DFP-10917 in patients with advanced CRC refractory to cytotoxic chemotherapy. Using the comet assay, DNA strand breakage in the whole blood samples was evaluated. We also investigated the relationship between expression of multiple tumor genes and efficacy of DFP-10917.

Methods

Patient eligibility

Eligible patients had pathologically confirmed advanced or locally advanced CRC that was refractory to standard treatment (at least two cytotoxic chemotherapy regimens containing a fluoropyrimidine, oxaliplatin, and irinotecan) and that progressed during or within 6 months of the most recent chemotherapy regimen. Eligible patients were ≥18 years old, had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, had at least one measurable tumor as defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0) [10], and did not receive chemotherapy for >3 weeks before study entry. All patients had adequate bone marrow function (defined as an absolute neutrophil count of ≥1,500/pL and a platelet count of ≥75,000/μL), adequate renal function (defined as a plasma creatinine level ≤1.5 × the institutional upper limit of normal [ULN]; if >1.5 mg/dL, a calculated creatinine clearance -by the Cockcroft-Gault method [11]-must have been ≥60 mL/min/1.73 m²), and adequate liver function (defined as a plasma total bilirubin level ≤1.5 × ULN and alanine transaminase and aspartate transaminase levels ≤2.5 × ULN; transaminase levels could be ≤5.0 × ULN if the patient had liver metastases). Immunocompromised patients, patients with central nervous system involvement, and pregnant or breastfeeding women were excluded. All patients provided written informed consent, and the protocol for this study was approved by the Institutional Review Board.

Study design

In this phase II, multicenter, single-arm, open-label study, patients received DFP-10917 until disease progression, occurrence of intolerable side effects, removal by the investigator, or withdrawal from the study.

This study used a two-stage design based on Simon's MinMax design to minimize the maximum sample size when the criteria for proceeding to the second stage were met [12]. The two-stage design consisted of 26 patients evaluable for efficacy in stage 1 and an additional 28 patients in stage 2 (if stage 1 was successful), for a total of 54 patients. If the study proceeded to stage 2, then the criteria for demonstrating sufficient efficacy to warrant further study at the end of stage 2 (end of the trial) were that at least 24 of 54 patients (44%) did not have progressive disease or did not die within 3 months of therapy.

Pretreatment evaluation and study locations

A complete medical history, including history of CRC and an electrocardiogram, was obtained at baseline (within 28 days before DFP-10917 administration). Computed tomography and magnetic resonance imaging studies of the chest, abdomen, and pelvis and target and non-target tumor measurements (RECIST) were obtained within 14 days of DFP-10917 administration, and physical examination and laboratory tests were obtained within 7 days before DFP-10917 administration. Patients were treated at three study sites: The Center for Cancer and Blood Disorders (Fort Worth, TX), The University of Texas MD Anderson Cancer Center (Houston, TX), and New York University Cancer Center (New York, NY).

Study treatment

All patients received DFP-10917 at 2.0 mg/m²/day by 14-day continuous central intravenous infusion, via an ambulatory pump for a 3-week treatment cycle (14-day continuous infusion and a 7-day rest period). Throughout the infusion, the DFP-10917 infusion bag was kept cold (<25°C) using a 12-oz frozen gel cold pack. The cold packs were replaced every 12 hours to ensure DFP-10917 stability during infusion. Patients returned to the infusion clinic on day 8 of each cycle to replace their DFP-10917 infusion bags.

Evaluation of efficacy and safety

We evaluated DFP-10917 efficacy for all patients who underwent at least two treatment cycles and had at least one post-treatment tumor assessment or for patients who discontinued DFP-10917 before tumor assessment owing to toxicity. Patients who completed fewer than two treatment cycles were also considered evaluable for drug efficacy as long as they showed clear evidence of disease progression. Tumor response and progressive disease were assessed after every two treatment cycles using RECIST. Patients were permitted to stay in the study if toxicity remained acceptable and tumor progression had not occurred [10]. All patients who received any amount of DFP-10917 were included in the safety analysis. Patients were evaluated by physical examination and laboratory testing at baseline, on day 8, and on day 15 of each cycle and within 72 hours before initiation of a subsequent cycle. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0 [13]. If a patient had more than one

adverse event within a category, the patient was counted in the category with the highest grade. If a patient had multiple occurrences of the same adverse event, the patient was counted once in the category of the highest grade.

Pharmacogenomics studies

Patient participation in exploratory pharmacogenomics studies was optional. There were 3 pharmacogenomics assessments in this study.

• **Tumor gene expression analysis**—We investigated the relationship between messenger ribonucleic acid (mRNA) expression levels of the following target genes in tumor tissues and efficacy of DFP-10917 (i.e. progression-free survival). The target genes to be analyzed were: deoxycytidine kinase (DCK), cytidine deaminase (CDA), equilibrative nucleoside transporter 1 (ENT1), solute carrier family 29 member 1 (SLC29A1), ribonucleotide reductase M1 polypeptide (RRM1), excision repair cross-complementing rodent repair deficiency, complementation group 1 (ERCC1), uracil-DNA glycosylase (UNG), mutL homolog 1 (MLH1), X-ray repair complementing defective repair in Chinese hamster cells 1/5 (XRCC1/5), proliferating cell nuclear antigen (PCNA), and APEX nuclease 1 (APEX1). The target genes outlined above were considered as possible candidate genes related to the efficacy of DFP-10917. For mRNA expression analysis, formalin-fixed paraffin-embedded (FFPE) specimens of tumor tissue were used. The mRNA levels of the target genes were determined by polymerase chain reaction (Gentris, Morrisville, NC) and relative gene expressions were reported using β -actin (ACTB) as the reference gene. mRNA expressions of activating to inactivating genes (DCK/CDA ratio) had been previously suggested to correspond with cytotoxicity of nucleoside analogs (such as gemcitabine) [20]. In this study, the association of the ratio with progression-free survival was evaluated.

• **Blood gene expression analysis**—The purpose of this analysis was to evaluate the relationship between mRNA expression levels of CDA in the blood and tumor tissues. The mRNA levels of CDA gene in both blood and tumor tissues were measured using polymerase chain reaction (Gentris, Morrisville, NC)

• **DNA strand break assessment**—For DNA damage analysis, blood samples from patients were collected at pre-dose (day 1) and on day 8, 15, and 22. The DNA strand breakage was measured using the comet assay (BioReliance, Rockville, MD). The comet assay (single cell gel electrophoresis) is a microgel electrophoretic technique that detects DNA damage in individual cells. The comet assay for the blood samples was performed under alkaline buffer condition (pH 13) with 20 minutes of unwinding time and 30 minutes of electrophoresis (0.7 V/cm) at 2–8°C under subdued light conditions. Two out of four slides from each sample were used for scoring and fifty cells per slide for a total of 100 cells per sample were scored. The level of DNA damage was measured by an automated scoring system (Comet Assay IV v 4.11), using the length and number of fragmented DNA that migrated outside the cell nucleus (comet tail). Tail intensity was defined as the percentage of DNA particles present in the tail. Pair-wise comparison (t-test) was used to compare the % tail intensity from the group mean of the vehicle controls and % tail intensity from the group mean of the positive control to determine acceptable criteria of a valid test [14, 15].

Statistical analysis

The primary endpoint for this trial was 3-month progression-free survival, defined as the proportion of patients who did not experience progressive disease or who did not die within 3 months of beginning therapy. All data summaries and listings were performed using SAS software, version 9.1 or higher. The Kaplan-Meier method was used to estimate overall survival rate. The Brookmeyer and Crowley method was used to determine the 95% confidence intervals (CI) for overall survival rates [16] Univariate Cox regression analysis was performed to determine the association of mRNA expressions with progression-free survival. All *p* values were 2-sided, and statistical significance was set at $p < 0.05$.

Results

Patient characteristics

Between 1/5/2009 and 11/25/2009, 28 patients were enrolled in this study and provided written informed consent. One patient withdrew from the study before receiving DFP-10917, and another did not meet initial screening criteria. A total of 26 patients received DFP-10917 and were included in study population. Table 1 shows the baseline characteristics of these patients. All 26 patients had received prior systemic therapy, at least 2 regimens of fluoropyrimidine, oxaliplatin, and irinotecan and progressed during or within 6 months following the most recent chemotherapy regimen. The mean patient age was 55.2 years (range, 41–74 years). Most of the patients were white and female. In most cases, the location of the primary colorectal lesion was the colon. Patients had received at least two previous cytotoxic chemotherapy regimens, and the mean time from CRC diagnosis to first DFP-10917 dose was approximately 3 years. Most patients had not received radiotherapy before enrolling in this study.

Exposure to study medication

All patients received at least one dose of DFP-10917 and were included in the safety analysis. A total of 23 (88%) patients began at least two cycles. Only seven patients (27%) initiated more than two cycles. Table 2 summarizes DFP-10917 exposure. During cycle 1, a total of 22 patients (85%) received 90% or more of the target dose (2.0 mg/m²/day). Over all cycles a total of 24 patients (92%) received 90% of the target dose and 25 (96%) received 75% of the target dose. The mean duration of all cycles (including cycles with dose delay) was 22.1 days.

Over all cycles, at least one daily dose of DFP-10917 was held during treatment for eight (31%) patients, and four (15%) patients had at least one reduction in DFP-10917 dose during the study. Among patients who received study drug for 2 cycles or more, there were 5 delays. The mean total dose of DFP-10917 per patient was 75.5 mg/m².

Efficacy

Of the 26 patients in stage 1, only three (12%) patients were progression free at 3 months. Thus, this study did not include a second stage, per the Simon two-stage design. No patients had a complete or partial response, and only six patients (23%) had stable disease. For most

patients (n=20, 77%), the best response was progressive disease. The median progression-free survival was 1.3 months (95% confidence interval, 1.3–1.6 months).

For the initial population (n=28) Kaplan-Meier analysis results showed that the 3-month overall survival rate was 77% (95% CI, 55.7–88.9%); the 6-month overall survival rate was 46.0% (95% CI, 24.1–65.4%); the 9-month overall survival rate was 39.4% (95% CI, 18.3–60.0%); and the 12-month overall survival rate was 39.4% (95% CI, 18.3–60.0%). Median overall survival for initial population was 5.5 months.

Adverse events

The most frequent DFP-10917-related toxicities for cycle 1 and all cycles are summarized in Table 3. During cycle 1, gastrointestinal adverse events were the most frequent toxicities (n=10, 38%). The most commonly reported grade 3 or higher adverse events in cycle 1 were hematologic events, gastrointestinal events, and fatigue. Similarly, the most frequent adverse events in all cycles were hematologic or gastrointestinal. During all cycles, hematologic toxicities were observed in 16 (62%) patients. Neutropenia was the most common hematologic toxicity (n=11, 42%) followed by anemia (n=7, 27%) and leukopenia (n=4, 15%). During all cycles, 14 (54%) patients experienced gastrointestinal toxicities. The most frequently reported gastrointestinal adverse events of any grade were nausea (n=8, 31%), diarrhea (n=7, 27%), and vomiting (n=4, 15%). Another frequent adverse event was fatigue (n=12, 46%). Frequently occurring (5%) DFP-10917-related, grade 3 or higher adverse events for all cycles were neutropenia (n=10, 38%), fatigue (n=4, 15%), anemia (n=3, 12%), and leukopenia (n=3, 12%). Three patients had grade 4 neutropenia, and one patient had grade 4 anemia. Two patients (8%) experienced serious gastrointestinal obstruction unrelated to DFP-10917, and they discontinued further treatment. The most frequent adverse events resulting in DFP-10917 interruption, delay, or dose reduction were neutropenia (n=6, 23%) patients and anemia (n=2, 8%). At the final assessment, no patients had better ECOG scores, 15 (58%) had no change in score, and 10 (38%) had worse scores than at baseline.

Pharmacogenomics results

Thirteen patients participated in pharmacogenomics study. mRNA expression of multiple target genes in tumor was evaluated but did not associate with progression-free survival (Supplemental Fig S1). Figure 1 demonstrates the correlation of progression-free survival with the ratio of DCK/CDA (i.e. activating to inactivating genes) in tumor tissues. Although in univariate Cox proportional hazard model the ratio of DCK/CDA was not significantly associated with progression-free survival ($p = 0.124$), both patients with stable disease showed DCK/CDA ratio of >3 . There was also no clear association between the levels of CDA in blood and tumor tissue (Supplemental Fig S2).

A total of 60 samples from 17 patients were evaluated for DNA strand breakage analysis. Thirteen patients had available results for comet assays on day 1 and 15. The results of comet assay and mean % tail intensity for each patient are shown in Figure 2. It was noted that with administration of DFP-10917, mean % tail intensity for each patient increased from day 1 to day 15 (medians of % tail intensity were 2.89 and 12.64 on day 1 and day 15, respectively, $p < 0.001$, sign test).

DISCUSSION

This is the first phase II clinical trial of single-agent DFP-10917 in patients with chemotherapy-refractory CRC. The 3-month progression-free survival rate failed to meet our criteria for continuing this single-agent trial. Our interim analysis revealed that only three of 26 patients were progression free at 3 months-below the pre-established futility boundary-so the trial was ended. No patients experienced a complete or partial response. The results of comet assay confirmed DNA breakage following infusion. Our study was unable to demonstrate any clear association between expression of target genes in tumor tissues and progression-free survival.

Overall, DFP-10917 did not show clinically meaningful single agent antitumor activity in chemotherapy-refractory advanced colorectal cancer. A possible explanation for DFP-10917's lack of activity in this trial is cross-resistance of this agent with oxaliplatin, 5-FU or other DNA-damaging agents in our heavily pre-treated patients. DFP-10917 might have greater activity alone, or in combination with other drugs, in patients with earlier-stage disease who have received less prior chemotherapy.

For patients with previously treated CRC, monotherapy with TAS-102 or regorafenib has shown a survival benefit but no meaningful improvement in response rates [17, 18]. In a phase III study of TAS-102, a nucleoside agent, assessment at least 6 weeks after randomization showed disease control in 44% of the patients who received TAS-102 and in 16% of the patients in the placebo group ($p<0.001$) [17]. Regorafenib, a novel multikinase inhibitor, demonstrated 6-week disease control in 41% of patients in a phase III trial, whereas only 15% of patients in the placebo group showed disease control ($p<0.0001$) [18]. In our population, only 27% of patients treated with DFP-10917 had disease control at 6 weeks.

In the toxicity analysis of DFP-10917, the most frequent medication-related adverse events were hematologic events, gastrointestinal events, and fatigue. Overall, this safety profile is similar to that observed in phase I clinical trials of DFP-10917 [9]. The most frequently observed grade 3 or 4 adverse events were neutropenia (38%), fatigue (15%), anemia (12%), and leukopenia (12%), similar to the toxicity profile of TAS-102, which also caused neutropenia in 38% of patients [17]. In contrast, the most frequently observed grade 3 or higher adverse events for regorafenib were hand-foot reaction (17%), fatigue (10%), diarrhea (7%), hypertension (7%), and rash/desquamation (6%) [18].

The trial is designed as an open-labeled, single arm study and there was no randomization. Therefore, a potentially meaningful benefit in disease control and/or overall survival compared to best supportive care cannot be excluded. Also, the sample size is small, which precludes precise estimates of disease control rate. The study report, which was delayed as the agent transferred between Taiho and DeltaFly, includes patients treated prior to the approval of regorafenib and trifluridine/tipiracil.

Recently, DFP-10917 has shown encouraging results as a salvage treatment in a phase I/II study of patients with relapsed or refractory acute myeloid leukemia (NCT01702155) [19]. In this study, patients received this agent by 14-day continuous infusion at the dose of 6.0

mg/m²/day, followed by 14-day rest. Although DFP-10917 was given at a higher dose compared to our study, it indicated a similar safety profile and was overall tolerated well. The main drug adverse events > grade 3 were: neutropenia (50%), thrombocytopenia (43%), and anemia (37%). Gastrointestinal side effects (43%) and fatigue (13%) were also frequent. In contrast to our study, a higher response rate (48%) was observed, a finding likely related to different histology and the higher dose of DFP-10917 administered in the patients.

Prior preclinical and phase I studies of DFP-10917 in patients with CRC demonstrated antitumor activity and given the negative result of this trial, further investigations of this agent should be undertaken in different settings-e.g. in patients with earlier stage disease, in combination with other agents or in different malignancies. Prolonged continuous infusion of DFP-10917 adds complexity to co-administering this agent with other drugs. In summary, DFP-10917 alone did not show meaningful antitumor activity in previously treated patients with chemotherapy-refractory advanced CRC. The safety profile of DFP-10917 was tolerable and similar to that observed in earlier clinical studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig 1.

Correlation of progression-free survival with the ratio of DCK/CDA (i.e. activating to inactivating genes) in tumor tissues (n= 13).

HR=0.720, $p=0.124$, Abbreviations: CDA, cytidine deaminase; DCK, deoxycytidine kinase; PD, progressive disease; SD, stable disease;

Fig 2.

The results of DNA damage analysis (comet assay) for patients with chemotherapy-refractory advanced colorectal cancer receiving DFP-10917 (n=13).

%; percentage

Table 1

Baseline characteristics of patients with chemotherapy-refractory advanced CRC (N=26) in a phase II study of DFP-10917 (2.0 mg/m²/day) given via 14-day continuous intravenous infusion.

Characteristic	Patients n (%) ^a
Sex	
Male	11 (42)
Female	15 (58)
Age (years)	
Mean (SD)	55.2 (10.34)
Range	41–74
Weight (kg)	
Mean (SD)	73.7 (19.312)
Range	42.5–131.6
Height (cm)	
Mean (SD)	166.4 (9.85)
Range	151–183
Body surface area ^b (m ²)	
Mean (SD)	1.813 (0.2597)
Range	1.35–2.49
Race	
White	20 (77)
Black	4 (15)
Asian	2 (8)
ECOG performance status score	
0	12 (46)
1	14 (54)
Time from diagnosis of CRC to first DFP-10917 dose (years)	
Mean (SD)	3.3 (1.53)
Median	3.1
Range	1–7
Primary CRC was resected	
Yes	22 (85)
No	4 (15)
Location of primary CRC	
Colon	25 (96)
Rectum	1 (4)
Prior resection of primary tumor	
Yes	22 (85)

Characteristic	Patients n (%) ^a
No	4 (15)
Prior radiotherapy	
Yes	3 (12)
No	23 (88)

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; CRC, colorectal cancer.

^aData are number of patients (%) unless otherwise indicated.

^bBody surface area (BSA) calculated using the DuBois formula: $BSA = (W^{0.425} \times H^{0.725}) \times 0.007184$.

Table 2

Exposure to study medication in patients with chemotherapy-refractory advanced colorectal cancer (N=26) in a phase II study of DFP-10917 (2.0 mg/m²/day) given via 14-day continuous intravenous infusion.

Exposure	Patients ^a n (%)
Cycles initiated	
1	26 (100)
2	23 (88)
3	7 (27)
4	6 (23)
5	3 (12)
6	3 (12)
>7	2 (8)
No. of cycles initiated per patient	
Mean (SD)	2.8 (2.19)
Median	2.0
Range	1–11
Received 90% of cycle 1 target DFP-10917 dose ^b	
Cycle 1	22 (85)
>1 cycle	19 (73)
Entire study	24 (92)
Received 75% of Cycle 1 target DFP-10917 dose ^b	
Cycle 1	25 (96)
>1 cycle	20 (77)
Entire study	25 (96)
DFP-10917 total dose administered (mg/m ²)	
Mean (SD)	75.5 (56.98)
Median	55.7
Range	15–289

Abbreviations: SD, standard deviation.

^aData are number of patients (%) unless otherwise indicated.

^bActual mg of DFP-10917 received × 100 divided by planned dose in mg, where the planned dose was determined by baseline body surface area and the number of dosing days (14 for each cycle).

Table 3

Adverse events in patients with chemotherapy-refractory advanced colorectal cancer (N=26) in a phase II study of DFP-10917 (2.0 mg/m²/day) given via 14-day continuous intravenous infusion.

	Cycle 1		All cycles		
Adverse event ^a	CTC Grade 1 or 2 n(%)	CTC Grade 3 n(%)	CTC Grade 1 or 2 n(%)	CTC Grade 3 n(%)	CTC Grade 4 n(%)
Total patients who experienced highest grade of adverse events	10 (38)	7 (27)	5 (19)	12 (46)	4 (15)
Hematologic	3 (12)	4 (15)	4 (15)	9 (35)	3 (12)
Anemia	2 (8)	1 (4)	4 (15)	2 (8)	1 (4)
Leukopenia		1 (4)	1 (4)	3 (12)	
Lymphopenia		1 (4)	2 (8)	1 (4)	
Neutropenia	1 (4)	2 (8)	1 (4)	7 (27)	3 (12)
Thrombocytopenia			3 (12)		
Gastrointestinal	10 (38)	2 (8)	12 (46)	2 (8)	
Constipation			1 (4)		
Diarrhea	4 (15)	1 (4)	6 (23)	1 (4)	
Nausea	6 (23)	1 (4)	7 (27)	1 (4)	
Stomatitis	1 (4)		2 (8)		
Vomiting	3 (12)		4 (15)		
General disorders	5 (19)	2 (8)	10 (38)	4 (15)	
Chills	2 (8)		2 (8)		
Fatigue	3 (12)	2 (8)	8 (31)	4 (15)	
Mucositis			1 (4)		
Infections	1 (4)	1 (4)	1 (4)	1 (4)	
Infection	1 (4)		1 (4)		
Pneumonia		1 (4)		1 (4)	
Metabolic and nutrition disorder	4 (15)		7 (27)		
Anorexia	3 (12)		6 (23)		
Dehydration	1 (4)		1 (4)		
Skin and musculoskeletal disorders	3 (12)		8 (31)		
Alopecia	1 (4)		6 (23)		
Erythema	1 (4)		1 (4)		
Arthralgia	1 (4)		1 (4)		
Nervous system disorders	3 (12)		3 (12)		
Headache	2 (8)		2 (8)		
Peripheral neuropathy	1 (4)		1 (4)		
Paresthesia	1 (4)		1 (4)		

	Cycle 1		All cycles		
Adverse event ^a	CTC Grade 1 or 2 n(%)	CTC Grade 3 n(%)	CTC Grade 1 or 2 n(%)	CTC Grade 3 n(%)	CTC Grade 4 n(%)
Respiratory and thoracic disorders	1 (4)		1 (4)		
Cough	1 (4)		1 (4)		
Other laboratory abnormalities	1 (4)	1 (4)	3 (12)		
Increased ALP		1 (4)	2 (8)		
Hypokalemia	1 (4)		1 (4)		

Abbreviations: CTC, Common Terminology Criteria [13]; ALP, alkaline phosphatase.

^a Adverse events reported were related to DFP-10917 as well as any events with missing relationship to DFP-10917.