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# A prospective phase II study of raltitrexed combined with S-1 as salvage treatment for patients with refractory metastatic colorectal cancer

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## Abstract

**Aim:** A third-line chemotherapy regimen for metastatic colorectal cancer (mCRC) is not available in China. Studies have shown that raltitrexed or S-1 has no complete cross-resistance with fluorouracil (5-FU). In this phase II study, we prospectively analyzed the efficacy and safety of raltitrexed combined with S-1 (RS regimen) in the treatment of mCRC after the failure of conventional chemotherapy.

**Methods:** A total of 105 patients with mCRC with progression following treatment with 5-FU, oxaliplatin, and irinotecan were enrolled between November 2015 and May 2019. Patients received intravenous infusion of raltitrexed (3 mg/m$^2$ from day 1 every 3 weeks) and oral S-1 (80-120 mg for 14 days every 3 weeks). Tumor evaluations were performed every two cycles according to the RECIST 1.1 guidelines.

**Results:** In the intention-to-treat patients, the objective response and disease control rates were 7.62% and 48.57%, respectively. The median progression-free survival and median overall survival were 2.5 and 8.0 months, respectively. Common adverse events included neutropenia, anemia, thrombocytopenia, and nausea, while neutropenia, anemia, thrombocytopenia nausea, diarrhea, skin eruption, and oral ulceration had grade 3 or higher adverse events. Subgroup analysis revealed that primary site or gene mutation status had little influence on the RS regimen efficacy, while the baseline albumin level, 5-FU administration in second-line therapy, and number of previous treatment regimens affected the efficacy.

**Conclusion:** The RS regimen demonstrated favorable effects in patients with mCRC following failure of standard chemotherapy, and could be a new choice for third-line treatment, and must be verified in future randomized clinical trials (Clinical trial: NCT02618356).

KEYWORDS
metastatic colorectal cancer, prospective phase II study, raltitrexed-S-1 combination, subgroup survival analysis, third-line chemotherapy regimen

## 1 | BACKGROUND

Colorectal cancer is one of the most common malignancies, and its incidence has gradually increased. Metastases are already present in 15-25% at the first diagnosis of colorectal cancer. Moreover, the proportion of patients who eventually progress to metastasis is high (50%).[1] For several decades, the main treatment for metastatic colorectal cancer (mCRC) has been fluorouracil (5-FU)-based chemotherapy as either the first- or second-line treatment.[2] The efficacy of 5-FU can be markedly improved when combined with calcium folinate (CF).[3] No other chemotherapeutic drugs were available for patients who experienced treatment failure with 5-FU, oxaliplatin, and irinotecan when the current clinical trial was conducted with raltitrexed and S-1 (RS regimen) in 2015. Although antiepidermal growth factor receptor monoclonal antibody (with or without irinotecan) and the multitarget inhibitor, regorafenib, can be used in mCRC as the third- or fourth-line treatment,[4] their use is restricted to approximately 50% of patients, those with the wild-type *Ras* gene, and they are expensive for some patients in China. Furthermore, regorafenib was not available in China at the time.

In vivo and in vitro studies demonstrated that raltitrexed or S-1 had no complete cross-resistance with 5-FU, and can be used in patients with mCRC who have had failure with 5-FU. Previous studies have reported that in patients who experienced failure with first-line therapy of 5-FU/CF, the overall response rate (ORR) of capecitabine as second-line therapy was 0%, whereas that of raltitrexed was 16%.[5] Deoxyuridylic acid is converted to deoxythymidine monophosphate in the cells by thymidylate synthase (TS). Approximately 85% of 5-FU is degraded and inactivated by dihydropyrimidine dehydrogenase (DPD). TS is a key enzyme in the metabolism of folic acid and is a target enzyme of 5-FU. Genetic variation in TS can affect the toxicity and efficacy of 5-FU, and inhibition of TS activity is an approach to overcome 5-FU resistance. Raltitrexed is a new-generation water-soluble TS inhibitor. In vitro studies have demonstrated a synergistic effect when raltitrexed was combined with 5-FU.[6] S-1 is a 5-FU derivative, which contains the active component-tegafur (FT207) and two biological modifiers, gimeracil (CDHP) and oteracil. CDHP is a DPD inhibitor that can inhibit the degradation of 5-FU, which is released from FT207 and catalyzed by DPD, and thereby maintains the effective concentration of 5-FU in the blood and tumor tissue for a prolonged duration, thus obtaining a similar effect to that of sustained intravenous infusion of 5-FU. The increase in DPD activity is one of the mechanisms of 5-FU resistance, so the inhibition of DPD activity is a strategy to overcome 5-FU resistance. Theoretically, as S-1 contains DPD inhibitor it may partially overcome the resistance of cancer cells to 5-FU. Thus, we hypothesized that the combination of raltitrexed and S-1, which is another 5-FU derivative, can improve the outcome of patients with mCRC when implemented as the third-line treatment.

Although oral regorafenib and fruquintinib—potent and highly selective vascular endothelial growth factor receptor inhibitors—are available in China and TAS-102—developed in Japan and will soon be available in China—can be used as third-line options in mCRC, their effects are still limited with a median overall survival (mOS) benefit of less than 2.7 months compared with the best suppurative care.[7,8] Moreover, some patients cannot benefit from regorafenib and fruquintinib, either because of the toxicity or high price. Given these reasons, new effective drugs or regimens must be developed to improve the survival of patients without the suitable choice of drugs. In our retrospective study, in 18 patients who had experienced failure with 5-FU, oxaliplatin, and irinotecan were treated with the RS regimen, we found a median progression-free survival (mPFS) and mOS of 2.5 and 7.0 months, respectively. The patients were well tolerant to the RS regimen, and most of the adverse events were graded 1-2.[9] Therefore, this prospective study was performed to further evaluate the efficacy and safety of the RS regimen in patients in whom conventional therapy had failed.

## 2 | PATIENTS AND METHODS

### 2.1 | Patient eligibility

This was a single-arm, two-center, prospective phase II trial. The main eligibility criteria were: ≥18 years of age; histologically confirmed adenocarcinoma of the colon or rectum; Eastern Cooperative Oncology Group (ECOG) 0-1; expected survival period ≥3 months; measurable objective tumor lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, ≥1; adequate blood test, hepatic and renal functions; and progression during or within 3 months following the last administration of approved standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan. All patients provided a written informed consent, and the study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center.

### 2.2 | Treatment

Raltitrexed 3 mg/m$^2$ intravenous infusion was administered once on the first day and was repeated every 3 weeks. The infusion time was about half an hour with antiemetics for premedication, including palonosetron and dexamethasone. S-1 was administered orally twice per day and was administered after breakfast and dinner. S-1 administration was continued for 2 weeks and discontinued for 1 week, and this was repeated every 3 weeks. The daily dose of S-1 was calculated according to the body surface area (BSA) <1.25 m$^2$, 80 mg/day; ≥1.25 to <1.5 m$^2$, 100 mg/day; ≥1.5 m$^2$, 120 mg/day. Treatment was continued until documented progression of disease (PD), intolerable toxicity, or unwillingness to continue treatment.

### 2.3 | Evaluation of efficacy and toxicity

Tumor evaluations were performed by computer tomography or magnetic resonance imaging every two cycles until disease progression

**TABLE 1** Patient baseline (ITT group, n = 105; PP group, n = 99)

| | ITT group (n = 105) | PP group (n = 99) |
|---|---|---|
| Gender | Male: 67 (63.81%) | Male: 62 (62.63%) |
| | Female: 38 (36.19%) | Female: 37 (37.37%) |
| Age | Median (25-75%): 60 (51-66) | Median (25-75%): 60 (51-66) |
| Line of systemic chemotherapy | 3 Line: 80 (76.19%) | 3 Line:76 people (76.77%) |
| | >3 Line: 25 people (23.81%) | >3 Line: 23 people (23.23%) |
| Primary tumor site | Right-sided colon: 25 (23.81%) | Right-sided colon: 23 (23.23%) |
| | Left-sided colon: 29 (27.62%) | Left-sided colon[†]: 27 (27.27%) |
| | Rectum: 50 (47.62%) | Rectum: 48 (48.48%) |
| | Unknown: 1 (0.95%) | Unknown: 1 (1.01%) |
| Primary tumor lesion | Exist: 28 (26.67%) | Exist: 26 (26.26%) |
| | None: 77 (73.33%) | None: 73 (73.74%) |
| Histological grade | Well (grade I): 0 (0.00%) | Well (grade I): 0 (0.00%) |
| | Moderate (grade II): 49 (46.67%) | Moderate (grade II): 46 (46.46%) |
| | Poor (grade III): 42 (40.00%) | Poor (grade III): 39 (39.39%) |
| | Unknown: 14 (13.33%) | Unknown: 14 (14.14%) |
| Gene status | Wild-type: 43 (40.95%) | Wild-type: 39 (39.39%) |
| | K-ras/N-ras mutation: 47 (44.76%) | K-ras/N-ras mutation: 45 (45.45%) |
| | B-raf mutation: 6 (5.71%) | B-raf mutation: 6 (6.06%) |
| | Unknown: 9 (8.57%) | Unknown: 9 (9.09%) |
| Number of metastatic sites | <3: 80 (76.19%) | <3: 76 (76.77%) |
| | ≥3: 25 (23.81%) | ≥3: 23 (23.23%) |
| Previous targeted therapy history | Yes: 62 (59.05%) | Yes: 58 (58.59%) |
| | No: 43 (40.95%) | No: 41 (41.41%) |
| 5-FU or capecitabine history in second-line chemotherapy | Yes: 60 (57.14%) | Yes: 56 (56.57%) |
| | No: 45 (42.86%) | No: 43 (43.43%) |

[†]In our study, left-sided colon only includes descending colon, sigmoid colon. The rectum was analyzed separately.

or intolerable toxicity. Short-term efficacy measures were complete response (CR), partial response (PR), stable disease (SD), and PD according to the RECIST 1.1 criteria. Toxicity was graded according to the United States National Cancer Institute Common Toxicity Criteria version 4.0. Blood tests were conducted weekly, and side effects were recorded.

### 2.4 | Endpoints and statistical analysis

Overall survival (OS) was defined as the time from inclusion to death due to any cause. Progression-free survival (PFS) was defined as the time from inclusion to PD. The ORR was defined as the rate of CR and PR, while the disease control rate (DCR) was defined as the rate of CR, PR, and SD. The primary endpoint was PFS, whereas the secondary endpoints were ORR, DCR, OS, and toxicity. Patients who provided the informed consent for the RS regimen were included in the intention-to-treat (ITT) population. The per-protocol (PP) population included patients who met the eligibility criteria, completed at least two chemotherapy cycles and one measurement according to the study protocol, while patients who stopped treatment or missed measurement because of adverse events or unwillingness were excluded. All of our statistical analyses were conducted using SPSS 23.0 (SPSS Inc., Chicago, IL) and R software 3.6.1 (https://www.r-project.org/). R packages survival and *survminer* were used for the survival analysis. The Kaplan-Meier curve and log-rank test were used to compare the PFS and OS between the subgroups. Pearson's chi-square test was used to compare the DCR between the subgroups. Two-sided *P*-values $< .05$ were considered statistically significant.

## 3 | RESULTS

### 3.1 | General information

In this study, 105 patients with advanced colorectal cancer between November 2015 and May 2019 in whom therapy with fluorouracil, oxaliplatin, or irinotecan had failed were included. All patients were pathologically confirmed to have colorectal adenocarcinoma and had complete imaging of at least one measurable lesion and

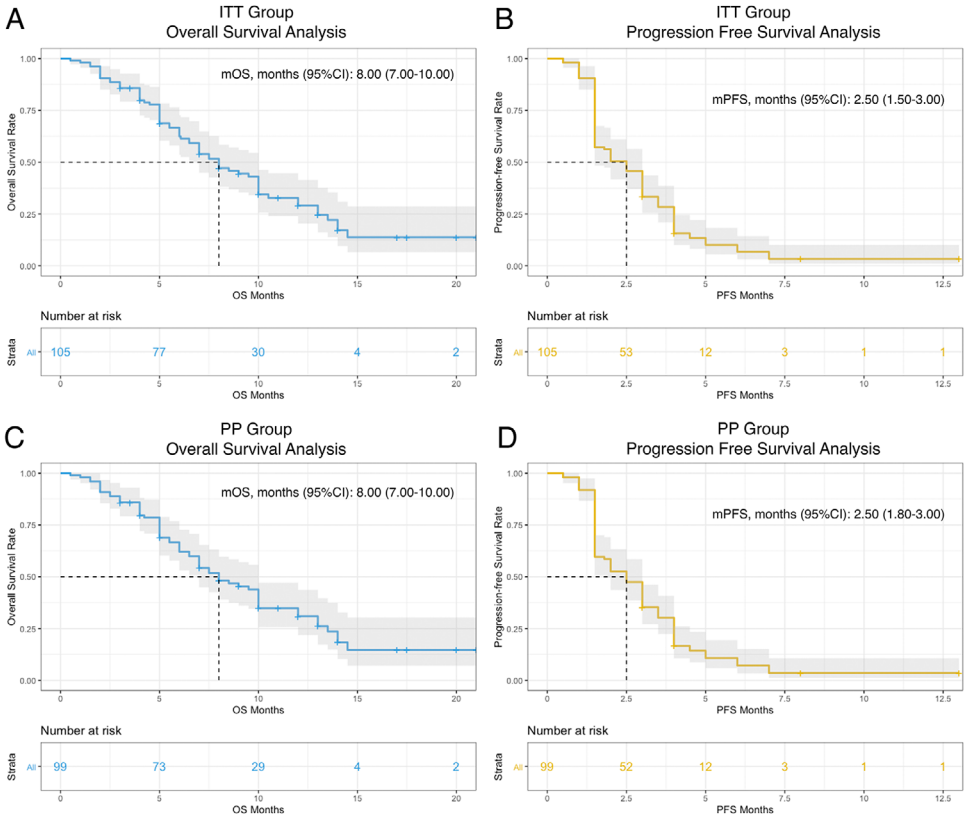


**FIGURE 1** Survival analysis of intention-to-treat (ITT) group and per-protocol (PP) group. A, Overall survival (OS) analysis of ITT group, medium progression-free survival (PFS) months (95% CI): 2.5 (1.5-3.0). B, PFS analysis of ITT group, medium OS months (95% CI): 8.0 (7.0-10.0). C, OS analysis of PP group, medium PFS months (95% CI): 2.5 (1.8-3.0). D, PFS analysis of PP group, medium OS months (95% CI): 8.0 (7.0-10.0) [Colour figure can be viewed at wileyonlinelibrary.com]

laboratory test data. All patients had previously received at least two-line chemotherapy without raltitrexed or S-1 and had no contraindications for chemotherapy. Among them, six patients received the regimen but did not complete the first assessment due to adverse events or unwillingness. The characteristics of the patients are given in Table 1.

## 3.2 | Effects

In the ITT population (105 patients), the ORR was 7.62%, and the DCR was 48.57%. The mPFS and mOS were 2.5 and 8.0 months, respectively. In the PP population (99 patients), the ORR was 8.08%, and the DCR was 51.52%. The mPFS and mOS were 2.5 and 8.0 months, respectively (Figure 1, Table S1).

## 3.3 | Adverse events

Adverse events (Table 2) included neutropenia, anemia, thrombocytopenia, abnormal liver enzymes, pyrexia, diarrhea, nausea, vomiting, anorexia, skin eruption, oral ulceration, and fatigue, and most of the adverse events were graded 1-2. The incidence of grade 3 hematological and nonhematological toxicities was 22.9%. The incidence of grade 4 hematological toxicity was less than 7% (7/105), comprising neutropenia, anemia, and thrombopenia.

## 3.4 | Subgroup analysis

Subgroup analysis of the ITT population is given in Table 3. The effects of the regimen were similar or not significantly different for the different pathological grades, primary lesions, different number of metastasis sites, with or without oncotarget therapy in the past, different primary site (left- or right-sided colon cancer, divided by colonic splenic flexure), even different gene mutation status (K-Ras/N-Ras mutant, B-Raf mutant, or wild-type mCRC). Patients with colon cancer appeared to have better PFS than those with rectum cancer, irrespective of left- or right-sided colon, with mPFS of 3.00 and 1.65 months, respectively (Figure 2A, $P = .044$). In the six patients carrying the *B-Raf* mutation, DCR was 50%, and mPFS was 2.75 months (Figure 2B). Patients with a metastatic site number less than 3 had a better OS and no difference in PFS (Figure 2C).

We found that patients with baseline albumin (ALB) >40 g/L had better mPFS and mOS (Figure 2D). The effects of the RS regimen were better when implemented as the third-line therapy than after third-line

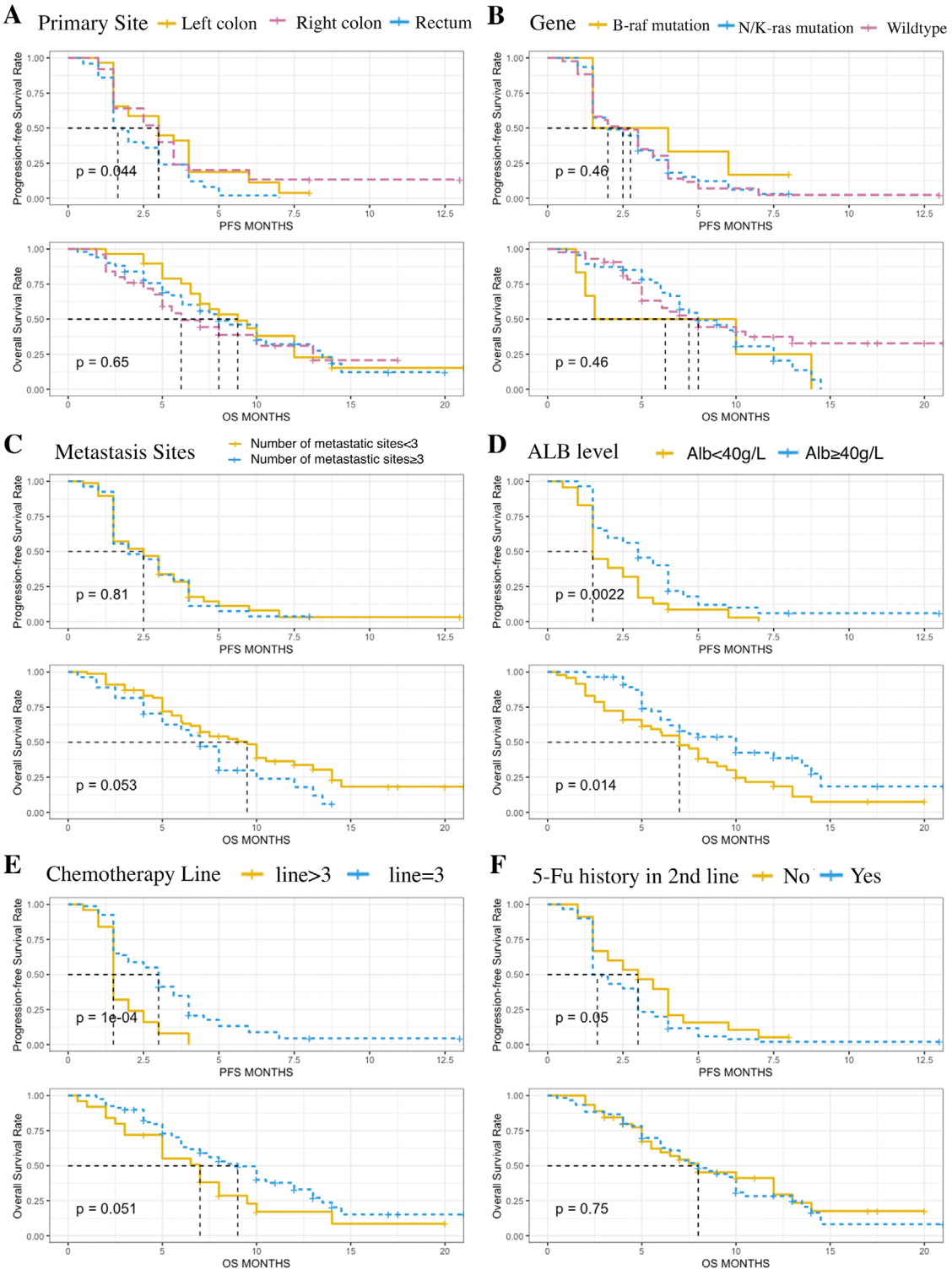


**FIGURE 2** Univariable survival analysis of primary site, gene status, metastatic site number baseline Alb, chemotherapy line and usage of 5-FU in second-line chemotherapy in intention-to-treat (ITT) group. A, Kaplan-Meier survival curve of progression-free survival (PFS) and overall survival (OS) according to primary site ($P = .044$, $P = .65$). B, Kaplan-Meier survival curve of PFS and OS according to gene status ($P = .46$, $P = .46$). C, Kaplan-Meier survival curve of PFS and OS according to number of metastatic sites ($P = .81$, $P = .053$). D, Kaplan-Meier survival curve of PFS and OS according to baseline Alb level ($P = .0022$, $P = .014$). E, Kaplan-Meier survival curve of PFS and OS according to line of chemotherapy ($P < .0001$, $P = .051$). F, Kaplan-Meier survival curve of PFS and OS according to usage of 5-FU in second-line chemotherapy ($P = .05$, $P = .75$) [Colour figure can be viewed at wileyonlinelibrary.com]

**TABLE 2** Adverse events

| Adverse event[a] | | Grade | Incidence (%) |
|---|---|---|---|
| Neutropenia | | All grades | 37.14 |
| | | Grade I | 15.24 |
| | | Grade II | 9.52 |
| | | Grade III | 8.57 |
| | | Grade IV | 3.81 |
| Anemia | | All grades | 45.71 |
| | | Grade I | 24.76 |
| | | Grade II | 13.33 |
| | | Grade III | 6.67 |
| | | Grade IV | 0.95 |
| Thrombocytopenia | | All grades | 20.95 |
| | | Grade I | 7.62 |
| | | Grade II | 7.62 |
| | | Grade III | 2.86 |
| | | Grade IV | 2.86 |
| Hepatic function abnormal | ALT | All grades | 5.71 |
| | | Grade I | 4.76 |
| | | Grade II | 0.95 |
| | AST | Grade I | 2.86 |
| | BIL | All grades | 1.90 |
| | | Grade I | 0.95 |
| | | Grade II | 0.95 |
| Nausea | | All grades | 21.90 |
| | | Grade I | 14.29 |
| | | Grade II | 5.71 |
| | | Grade III | 1.90 |
| Diarrhea | | All grades | 8.57 |
| | | Grade I | 5.71 |
| | | Grade II | 1.91 |
| | | Grade III | 0.95 |
| Skin eruption | | All grades | 8.57 |
| | | Grade I | 6.67 |
| | | Grade II | 0.95 |
| | | Grade III | 0.95 |
| Vomiting | | Grade I | 7.62 |
| Pyrexia | | All grades | 6.67 |
| | | Grade I | 4.76 |
| | | Grade II | 1.90 |
| Fatigue | | All grades | 6.67 |
| | | Grade I | 5.72 |
| | | Grade II | 0.95 |
| Oral ulceration | | All grades | 4.87 |
| | | Grade I | 1.91 |
| | | Grade II | 0.95 |
| | | Grade III | 1.91 |

*Note*. Rare adverse event was defined as incidence <3%. Other rare adverse events: hand-foot syndrome, baldness, headache, epistaxis, edema of lower extremity.

[a]We reported adverse events with all-grade incidence >5%, or grade 3-4 adverse events happened in detail.

treatment (Figure 2E). If 5-FU or capecitabine was not used as the second-line treatment, the patients had a mPFS of 3.0 months, which was significantly longer than the mPFS of 1.9 months in continuous 5-FU treatment patients (Figure 2F, $P = .05$). Additionally, no difference in second-line PFS was found when either 5-FU or capecitabine was used as the second-line treatment, there was mPFS of 4.0 months in both groups (irinotecan single-drug group and FOLFIRI or irinotecan combined with capecitabine regimen group; Figure S1, $P = .27$).

## 4 | DISCUSSION

A number of phase II and III clinical trials have shown that the efficacy of raltitrexed monotherapy for mCRC is comparable with that of 5-FU/CF.[10] Yu et al used raltitrexed alone as second-line therapy for the treatment of mCRC, and the ORR was 28.6% and mPFS was 6.5 months.[11] The promising efficacy of raltitrexed monotherapy has promoted the study of combination regimens with raltitrexed. Gravalos et al compared the effects of TOMOX (oxaliplatin combined with raltitrexed) and FOLFOX4 regimen as first-line therapy in the treatment of mCRC, and no significant differences in the OS, PFS, and remission time between the two regimens were observed.[3] Wang et al reported a randomized controlled phase III clinical trial of raltitrexed compared with 5-FU/CF combined with oxaliplatin in the treatment of mCRC, which included chemotherapy-naive (first-line) patients or patients in whom 5-FU-based regimen had failed, and found that in 5-FU-based regimen-failed patients, the ORR in the raltitrexed plus oxaliplatin group was significantly higher than that in the 5-FU/CF plus oxaliplatin group (29.4% vs 12.8%, $P = .0448$).[12] These results indicated that the effects of raltitrexed were similar to 5-FU in the first-line treatment, but the efficacy of the raltitrexed-based combination regimen was superior to that of the 5-FU-based combination regimen after the failure of first-line 5-FU treatment, suggesting the absence of complete cross-resistance between raltitrexed and 5-FU. Raltitrexed has been approved for the treatment of patients with mCRC who are unsuited for 5-FU treatment (including resistant or intolerant to 5-FU) in China. Furthermore, studies reported that the ORR of S-1 monotherapy as second-line treatment in patients with failed 5-FU and irinotecan therapy was 7% and mPFS was 2.8 months; this is comparable to the standard second-line FOLFIRI regimen with ORR approximately 4% in patients with failed 5-FU-based combination regimens. The results confirmed that S-1 could partially overcome 5-FU resistance and may still be effective for some patients with failed second-line treatment 5-FU. However, the ORR of S-1 as the third-line treatment for 5-FU, irinotecan, and oxaliplatin-failed mCRC was 0%,[13] indicating the weak effects of S-1 monotherapy as the third-line.

These studies suggest that raltitrexed or S-1, targeting TS, have no complete cross-resistance with 5-FU, and may be used for patients with mCRC following failure of 5-FU treatment. However, for patients who failed 5-FU, irinotecan, and oxaliplatin, the efficacy of raltitrexed or S-1 monotherapy as third-line therapy is weak and limited. Vakhabova et al reported that raltitrexed in combination with xeloda as first-line treatment was effective in 75% of patients, with mPFS of 6.3 months and

**TABLE 3** Subgroup analysis of disease control rate (DCR), progression-free survival (PFS), and overall survival (OS) in ITT group

| | | Numbers | DCR | Median PFS | Median OS |
|---|---|---|---|---|---|
| Overall | | 105 | 48.57% | 2.50 | 8.00 |
| Gender | | | $P = .490$ | $P = .32$ | $P = .12$ |
| | Female | 38 | 52.63% | 2.25 | 10.00 |
| | Male | 67 | 46.27% | 2.50 | 7.00 |
| Age | | | $P = .918$ | $P = .77$ | $P = .52$ |
| | <60 | 49 | 49.98% | 2.00 | 8.00 |
| | ≥60 | 56 | 48.21% | 2.50 | 8.00 |
| Histological grade | | | $P = .480$ | $P = .13$ | $P = .74$ |
| | II | 47 | 42.94% | 2.0 | 7.00 |
| | III | 42 | 52.38% | 3.0 | 8.50 |
| | Unknown | 14 | 42.86% | 1.5 | 7.25 |
| Gene | | | $P = .978$ | $P = .46$ | $P = .46$ |
| | Wild-type | 43 | 48.84% | 2.50 | 7.50 |
| | K-ras/N-ras mutation | 47 | 51.06% | 2.00 | 8.00 |
| | B-raf mutation | 6 | 50.00% | 2.75 | 6.25 |
| Primary tumor site | | | $P = .006$ | $P = .044$ | $P = .65$ |
| | Right-sided colon | 25 | 56.00% | 3.00 | 6.00 |
| | Left-sided colon | 29 | 68.97% | 3.00 | 9.00 |
| | Rectum | 50 | 34.00% | 1.65 | 8.00 |
| Primary tumor resection | | | $P = .465$ | $P = .37$ | $P = .21$ |
| | No | 28 | 53.57% | 3.00 | 6.07 |
| | Yes | 77 | 46.75% | 2.00 | 8.00 |
| Number of metastasis site | | | $P = .116$ | $P = .81$ | $P = .053$ |
| | <3 | 77 | 53.25% | 2.50 | 9.50 |
| | ≥3 | 27 | 37.04% | 2.00 | 7.00 |
| Baseline ALB | | | $P = .016$ | $P = .0022$ | $P = .014$ |
| | <40 g/L | 47 | 34.04% | 1.50 | 7.00 |
| | ≥40 g/L | 57 | 59.65% | 3.00 | 10.00 |
| Baseline HB | | | $P = .484$ | $P = .14$ | $P = .061$ |
| | <115 g/L | 36 | 41.67% | 1.50 | 6.07 |
| | ≥115 g/L | 68 | 51.47% | 2.75 | 8.50 |
| Targeted therapy history | | | $P = .935$ | $P = .93$ | $P = .69$ |
| | Yes | 62 | 48.39% | 2.00 | 8.00 |
| | No | 43 | 48.84% | 2.50 | 7.50 |
| 5-FU or capecitabine history in second-line therapy | | | $P = .140$ | $P = .05$ | $P = .75$ |
| | Yes | 60 | 41.67% | 1.65 | 8.00 |
| | No | 45 | 57.78% | 3.00 | 8.00 |
| Number of systemic therapy | | | $P = .001$ | $P < .001$ | $P = .051$ |
| | 3 Line | 80 | 57.50% | 3.00 | 9.00 |
| | >3 Line | 25 | 20.00% | 1.50 | 7.00 |

mOS of 18.2 months in responsive patients.[14] The efficacy of the combination regimen in this study was superior to the reported efficacy of raltitrexed or xeloda monotherapy in the literature, preliminarily suggesting that the combination of raltitrexed and 5-FU or its derivative may improve the efficacy.

In the present study, we prospectively analyzed the efficacy and safety of RS regimen in the treatment of mCRC after failure of second-line therapy. In 105 patients following this regimen, the mPFS and mOS was 2.5 and 8.0 months, similar to the effects of regorafenib in CONCUR study with mPFS of 3.2 months and mOS of 8.8 months,[15] and in CORRECT study with mPFS of 1.9 months and mOS of 6.4 months,[16] and TAS of 102 in TERRA study with mPFS of 2.0 months and mOS of 7.8 months,[3] supporting the improved efficacy of this combination regimen.

Recently, Chen et al reported similar results (ORR, 13.0%; mPFS, 107 days; mOS, 373 days) in their phase II clinical trial with the same RS regimen for refractory mCRC, which included 46 patients and started at the same time as our phase II study in 2015.[17] This regimen began as a third-line treatment for mCRC earlier in February 2014, and the results of our retrospective study with the regimen were accepted in the 2017 ASCO abstract.[9] As we enrolled many more patients in this phase II trial (n = 105), we performed subgroup and prognostic factor analysis to help identify the beneficial population.

In the subgroup analysis, we found that irrespective of the pathological grade, the location of the primary lesion, the number of metastatic sites, the mutation status of *Ras* and *B-Raf* genes, and the history of target therapy, the RS regimen was similar to that of the patients with mCRC. Subgroup analysis showed that the RS regimen had similar effects on left- or right-sided colon cancer and *B-Raf* mutant or wild-type cancer, indicating that the RS regimen may be suitable for various kinds of mCRC, which should be verified in future randomized clinical trials. Colon cancer irrespective of right-sided or left-sided cancer demonstrated better PFS than rectal cancer, but showed little difference in OS. Known as poor-prognosis, right-sided colon cancer showed similar efficacy to left-sided colon cancer in our study. Although whether the effects of the RS regimen vary with the primary site requires investigation, the results indicated a potential choice for right-sided colon cancer in third-line treatment. In the SWOG 1406 study, the mPFS of the vemurafenib + irinotecan + cetuximab (VIC) regimen in *V600E* mutant mCRC cases was 4.3 months, which showed relatively better effects for poor-prognosis *B-Raf* mutant mCRC cases.[18] However, the VIC regimen is very expensive, and most patients in China find it unaffordable. Our study showed that the RS regimen had mPFS of 2.75 months in *B-Raf* mutant mCRC cases, which suggested a possibly effective and more economical third-line treatment option for *B-Raf* mutant mCRC cases. However, because of the limited population, the effects of the RS regimen on *B-Raf* mutant patients must be verified by further clinical trials with larger sample sizes.

The results showed that the efficacy of RS regimen used in the third-line treatment was better than that after third-line therapy.[19] We also found that patients with baseline ALB ≥40 g/L were associated with better efficacy and prognosis, suggesting that the chemotherapy efficacy might be related to the nutritional status of patients, and also provided a reference for the selection of RS regimen beneficiaries. The PFS of the third-line treatment with the RS regimen was influenced by the use of 5-FU or capecitabine in second-line treatment as irinotecan single-drug regimen group that outperformed the FOLFIRI or irinotecan combined with capecitabine regimen group, with mPFS of 3.0 and 1.9 months, respectively, suggesting that continuous 5-FU, applications in second-line treatment after first-line 5-FU-based chemotherapy might increase the resistance to the RS regimen. We also found that there was no difference in second-line PFS between the irinotecan single-drug regimen group and FOLFIRI or irinotecan combined with capecitabine regimen. These findings suggest that it might be better if 5-FU was discontinued in the second-line treatment.

In conclusion, our study provides a new economical, tolerable, and effective regimen for refractory mCRC after failure of conventional therapy. The treatment was well tolerated, and most of the adverse events were mild or moderate. For usually poor-prognosis, right-sided colon, primary, or *B-Raf* mutant mCRC, the RS regimen showed similar effects when compared to left-sided colon or wild-type mCRC in our study. These results indicated that the RS regimen may be suitable for various kinds of mCRC, including known poor-prognosis, right-sided colon cancer, and *B-Raf* mutant cancer. The effects of this new regimen must be confirmed through future randomized clinical trials.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHOR CONTRIBUTIONS

Conceptualization: Weijian Guo. Project administration and resource: WeiJian Guo Mingzhu Huang, Yusheng Wang, Xiaodong Zhu, Zhiyu Chen, Wen Zhang, Chenchen Wang, Xiaowei Zhang, LixinQiu, Zhe Zhang, Xiaoying Zhao, and Wenhua Li. Data curation: Mingzhu Huang, Yusheng Wang, and Yue Yang. Data analysis: Yue Yang. Writing-original draft: Mingzhu Huang and Yue Yang. Writing-review and editing: Weijian Guo.

## ETHICS STATEMENT

This study is registered with ClinicalTrials.gov, number: NCT02618356. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Fudan University Shanghai Cancer Center and Shanxi Cancer Hospital, and a signed informed consent was obtained from all the participants.

## DATA AVAILABILITY STATEMENT

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

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## REFERENCES

1. Van Cutsem E, Nordlinger B, Cervantes A, et al. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol*. 2010;21(Suppl 5):v93-v97.
2. Tournigand C, Andre T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*. 2004;22:229-237.
3. Gravalos C, Salut A, Garcia-Giron C, et al. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. *Clin Transl Oncol*. 2012;14:606-612.
4. Nappi A, Berretta M, Romano C, et al. Metastatic colorectal cancer: role of target therapies and future perspectives. *Curr Cancer Drug Targets*. 2018;18:421-429.
5. Hoff PM, Pazdur R, Lassere Y, et al. Phase II study of capecitabine in patients with fluorouracil-resistant metastatic colorectal carcinoma. *J Clin Oncol*. 2004;22:2078-2083.
6. Avallone A, Di Gennaro E, Bruzzese F, et al. Synergistic antitumour effect of raltitrexed and 5-fluorouracil plus folinic acid combination in human cancer cells. *Anticancer Drugs*. 2007;18:781-791.
7. Xu J, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study. *J Clin Oncol*. 2018;36:350-358.
8. Li J, Qin S, Xu RH, et al. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: the FRESCO randomized clinical trial. *JAMA*. 2018;319:2486-2496.
9. Guo WJ, Wu ZH, Huang MZ, et al. A retrospective study of raltitrexed combined with S-1 as salvage treatment for patients with metastatic colorectal cancer after failure of standard chemotherapy. *J Clin Oncol*. 2017;35:e15066.
10. Yasui H, Yoshino T, Boku N, et al. Retrospective analysis of S-1 monotherapy in patients with metastatic colorectal cancer after failure to fluoropyrimidine and irinotecan or to fluoropyrimidine, irinotecan and oxaliplatin. *Jpn J Clin Oncol*. 2009;39:315-320.
11. Yu JW. The observation of raltitrexed as second-line chemotherapy for advanced colorectal cancer. *Chin J Mod Drug Appl*. 2012;6:18-19.
12. Wang JL, Li J, Qin SK, et al. Randomized multicenter phase III trial of oxaliplatin plus raltitrexed verus oxaliplatin plus fluorouracil and leucovorin for advanced colorectal cancer. *Chin Clin Oncol*. 2012;17:6-11.
13. Yasui H, Yoshino T, Boku N, et al. Retrospective analysis of S-1 monotherapy in patients with metastatic colorectal cancer after failure to fluoropyrimidine and irinotecan or to fluoropyrimidine, irinotecan and oxaliplatin. *Jpn J Clin Oncol*. 2009;39:315-320.
14. Vakhabova JV, Semenov NN, Dobrova NV, et al. Clinical study of combined use of tomudex (raltitrexed) and xeloda (capecitabine) as first-line treatment for patients with metastasizing colorectal cancer. *Bull Exp Biol Med*. 2008;145:249-251.
15. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16:619-629.
16. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381:303-312.
17. Chen Y, Wu J, Cheng K, et al. S-1 plus raltitrexed for refractory metastatic colorectal cancer: a phase II trial. *Oncologist*. 2019;24:591.
18. Kopetz S, McDonough SL, Lenz HJ, et al. Randomized trial of irinotecan and cetuximab with or without vemurafenib in BRAF-mutant metastatic colorectal cancer (SWOG S1406). *J Clin Oncol*. 2017;35:520.
19. Tsuji Y, Shitara K, Yamanaka T, et al. REVERCE: randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for metastatic colorectal cancer patients previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-Biomarker analysis. *J Clin Oncol*. 2018;36:3510.

## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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