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The Innovation Oncology

Efficacy and safety of fruquintinib plus chemotherapy as second-line therapy in metastatic colorectal cancer: A multicenter trial

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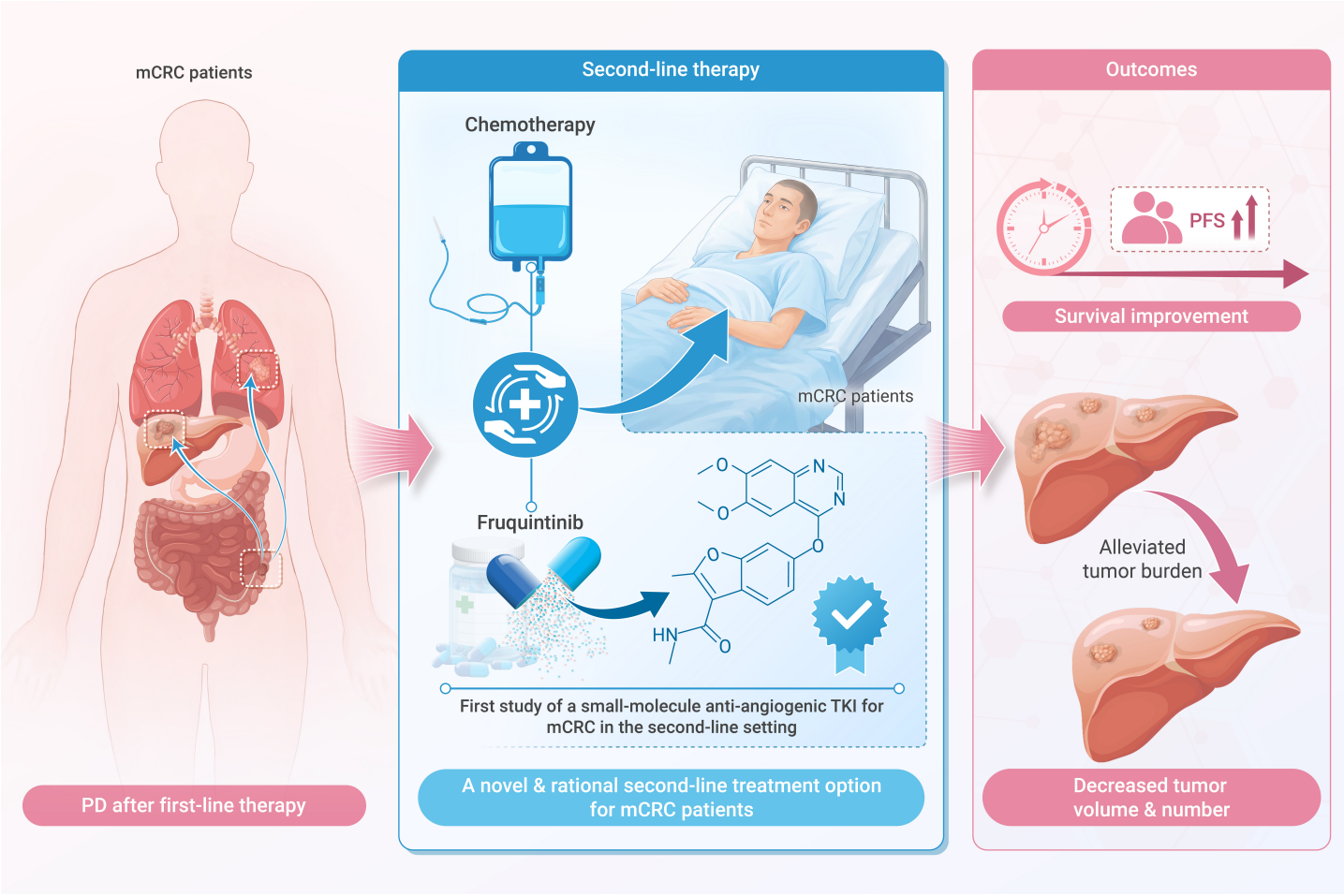
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- We evaluated fruquintinib plus chemotherapy as second-line therapy in metastatic colorectal cancer (mCRC).
- It is the first study of a small-molecule tyrosine kinase inhibitor for mCRC patients at second-line setting.
- The real-world mCRC patients with second-line treatment were screened for propensity score matching analysis.
- Results showed progression-free survival benefit and favorable safety profile compared to real-world data.
- Fruquintinib plus chemotherapy may represent a novel and rational second-line treatment option for mCRC.

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To evaluate the efficacy and safety of fruquintinib combined with chemotherapy as second-line treatment for metastatic colorectal cancer (mCRC), we performed an open-label phase II trial. A total of 102 Chinese mCRC patients who progressed after first-line therapy were enrolled and received fruquintinib plus chemotherapy. Fruquintinib was administered in a standard 4-week regimen or an adjusted 3-week regimen. Primary endpoint was progression-free survival (PFS). Efficacy and adverse events (AEs) were compared to a real-world control group. As of data cutoff on January 10, 2026, with a median follow-up of 33.2 months, the median PFS was 7.1 months (95% CI, 5.4-8.6) and overall survival (OS) was 22.6 months (95% CI, 19.7-26.2). Objective response rate was 27.6% (95% CI: 19.2-37.7), disease control rate (DCR) was 83.7% (95% CI: 74.5-90.1), and median duration of response (DoR) was 11.9 months (95% CI: 8.8-15.0). Patients with primary tumor resection, no liver metastasis, or no prior history of anti-vascular endothelial growth factor (receptor) therapy had improved survival. Grade ≥ 3 AEs occurred in 38.2% of patients, common grade ≥ 3 AEs were neutropenia (11.8%) and leukopenia (5.9%). Compared to the control group, the fruquintinib group showed significantly improved median PFS (6.6 vs. 5.3 months; HR, 0.68, 95% CI, 0.51-0.91; P = 0.010), higher ORR (23.1% vs. 16.9%) and DCR (79.5% vs. 67.7%), and a numerically longer OS (23.0 vs. 19.7 months; P = 0.640). These results showed fruquintinib plus chemotherapy may represent a novel and rational second-line option for mCRC with promising efficacy and favorable safety.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer globally, with over 900,000 deaths estimated in 2020.[1] According to the Global Cancer Observatory 2020, it presents the highest total lifetime risk among gastrointestinal cancers, accounting for 38.5% of developing and 28.2% of dying from these malignancies.[2] In China, CRC incidence and mortality have risen steadily since 2000, reaching 517,100 new cases and 240,000 deaths in 2022.[3]

For metastatic CRC (mCRC), fluorouracil-based doublet or triplet chemotherapy combined with VEGF(R) or EGFR inhibitors remains the standard first- and second-line treatment.[4-6] Phase III trials (VELOUR, BEBYP, ML18147, RAISE) have demonstrated that adding anti-VEGF(R) agents to chemotherapy in the second-line setting improves progression-free survival (PFS), supporting the strategy of continued angiogenesis inhibition beyond first-line therapy.[7-11] Despite this, median PFS for second-line mCRC treatment is limited to approximately 5-6 months, and treatment-related adverse events (TRAEs), including infusion-related and allergic reactions, are frequent. Consequently, enhancing efficacy while reducing toxicity in second-line therapy remains a critical issue.

Orally administered small-molecule anti-angiogenic inhibitors, such as regorafenib and fruquintinib, have shown significant survival benefits in later-line mCRC treatment.[12,13] Fruquintinib, a highly selective VEGFR inhibitor, has demonstrated favorable tolerability and efficacy both as monotherapy and in combination regimens in mCRC, based on reported data and clinical experience.[13-16] However, its role specifically as a second-line targeted agent in mCRC has not been established. But for Chinese patients with advanced gastric cancer, fruquintinib had been used in combination with paclitaxel as a second-line therapy with favorable PFS of 4-5 months and objective response rate (ORR) of 25.9%-44.7%.[17,18] In addition, first-line or second-line fruquintinib therapy was also an effective regimen for unresectable or metastatic soft-tissue sarcoma, with a median PFS of 7.4 months and ORR of 25.8%.[19] Furthermore, compared with many first-generation small-molecule VEGFR inhibitors (sunitinib, sorafenib), fruquintinib showed superior potency and kinase selectivity.[20,21] Another factor that cannot be ignored is China's socio-economic conditions. Within the coverage of medical insurance, fruquintinib is cheaper than bevacizumab and is also more convenient to be administered orally. Therefore, to address this unmet therapeutic needs of mCRC patients, we performed this study to prospectively evaluate the efficacy and safety of fruquintinib combined with chemotherapy as second-line treatment for mCRC.

MATERIALS AND METHODS

Study design and participants

This multicenter, open-label, phase 2 trial was conducted at 12 sites in China. Eligible patients were aged ≥ 18 years with histologically and/or cytologically confirmed CRC. Key inclusion criteria comprised: disease progression, unacceptable toxicity leading to discontinuation of first-line standard chemotherapy (with or without targeted therapy), or relapse < 6 months after completing adjuvant chemotherapy; at least one measurable target lesion per

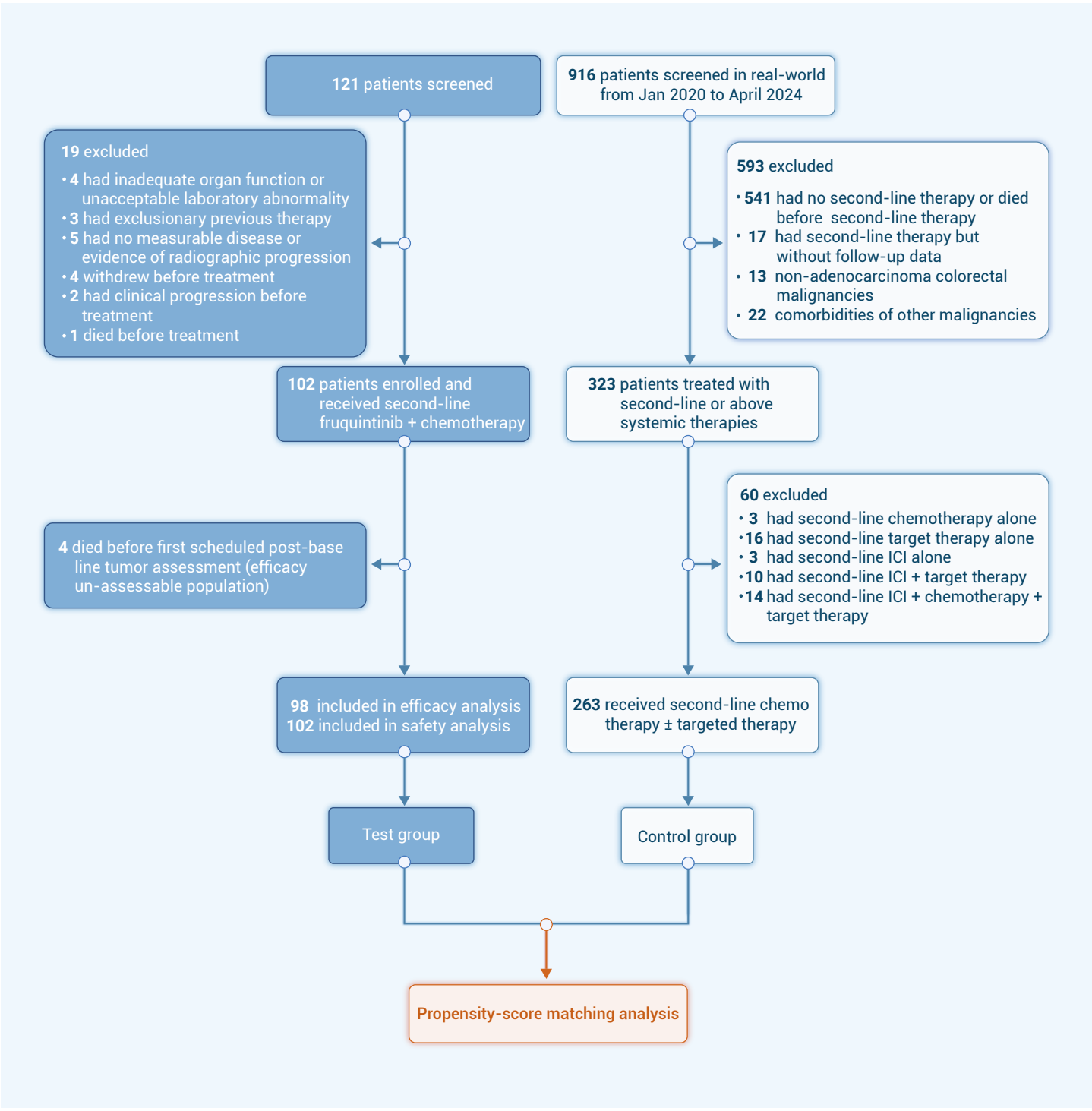


Figure 1. Trial flowchart.

RECIST version 1.1; Eastern Cooperative Oncology Group performance status (ECOG PS) of 0-2; life expectancy ≥ 3 months; and adequate organ function. Key exclusion criteria included: prior fruquintinib treatment; major surgery within 28 days or radiotherapy within 14 days of study entry; thrombotic or hemorrhagic event within 6 months; other malignancies within 5 years, severe cardiovascular disease (NYHA class ≥ II, uncontrolled arrhythmia, recent myocardial infarction), active uncontrolled infections including COVID-19 at screening; conditions impairing oral drug absorption. Microsatellite instability (MSI) or mismatch repair (MMR) status was tested using immunohistochemistry and/or polymerase chain reaction or next-generation sequencing at each site.

The study protocol received approval from the institutional review board at each participating center and was registered on Chictr.org.cn (identifier: ChiCTR2200059280). The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice guidelines, and applicable local regulations. All participants provided written informed consent prior to enrollment. This manuscript adheres to CONSORT reporting guidelines.

Treatment procedures and end points

Fruquintinib was administered orally at a starting dose of 5 mg once daily on a schedule of 3 weeks on treatment followed by 1 week off. The second-line chemotherapy regimen, chosen by the investigator, consisted of fluo-

Table 1. Baseline patient characteristics (N = 102).

Characteristic	Patients, No. (%)
Age, median (IQR), year	63 (56-71)
> 60	55 (53.9)
≤ 60	47 (46.1)
Sex	
Male	63 (61.8)
Female	39 (38.2)
ECOG PS score	
0-1	95 (93.1)
2	7 (6.9)
Primary tumor location	
Left-sided	79 (77.5)
Right-sided	23 (22.5)
Type of metastasis	
With liver metastasis	58 (56.9)
With lung metastasis	42 (41.2)
Previous treatment	
Chemotherapy	102 (100.0)
Surgery	88 (86.3)
Radiotherapy	32 (31.4)
Anti-EGFR therapy	9 (8.8)
Anti-VEGF(R) therapy	56 (54.9)
RAS/BRAF status	
Mutant type	37 (36.3)
Wild type	43 (42.2)
Unknown	22 (21.6)
MSI status	
MSS/pMMR	102 (100.0)
MSI-H/dMMR	0

Abbreviations: dMMR, mismatch repair deficiency; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IQR, interquartile range; MSI, microsatellite instability; MSI-H, high microsatellite instability; MSS, microsatellite stable; pMMR, mismatch repair proficient; VEGF(R), vascular endothelial growth factor (receptor).

rouracil-based therapy (e.g., leucovorin/fluorouracil, capecitabine, or raltitrexed), irinotecan, and/or oxaliplatin. Typically, patients who received first-line oxaliplatin were switched to irinotecan-based therapy in the second line, and vice versa. Treatment continued for up to 8 courses of chemotherapy, followed by fruquintinib maintenance therapy until disease progression, death, unacceptable toxicity, patient's withdrawal of consent, or investigator's decision to discontinue. Dose modifications and assessment procedures followed the study protocol, mainly involving the discontinuation and reduction of chemotherapy and fruquintinib. The dose reduction of fruquintinib was mainly from 5 mg to 4 mg daily or further to 3 mg daily. Meanwhile, the administration mode of fruquintinib would also be adjusted from the standard 3 weeks on/1 week off (4-week regimen) to 2 weeks on/1 week off (3-week regimen) based on investigator's choice, patient-reported outcomes, ECOG PS score and patient compliance.

The primary endpoint was PFS, defined as the time from enrollment to disease progression or death from any cause. Secondary endpoints included: ORR: proportion of patients achieving a confirmed complete response (CR) or partial response (PR); disease control rate (DCR): proportion of patients achieving CR, PR, or stable disease (SD); overall survival (OS): time from enrollment until death from any cause, and duration of response (DoR). Subgroup analysis was also performed to screen beneficial population.

All participants receiving at least one dose of study treatment were included in efficacy and safety analyses. Tumor response was assessed every 2 months using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Safety assessments, conducted throughout the study, included monitoring adverse events (AEs), laboratory abnormalities, vital signs, electrocardiograms, and ultrasound examinations. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0. At scheduled visits, investigators recorded the severity, duration, relationship to study medication, and outcome of all AEs based on clinical assessment.

Propensity score matching (PSM) comparison

As this non-randomized trial did not include a concurrent control group receiving standard second-line therapy, we performed an exploratory post-hoc analysis comparing outcomes in our cohort against a historical cohort of similar patients with mCRC. This comparator cohort received second-line therapy at the same institution between January 2020 and April 2024. To minimize potential confounding, we balanced the groups using PSM (1:2 ratio; caliper = 0.02) based on the following baseline variables: age, sex, ECOG PS, primary tumor location, presence of liver metastasis, MSI status, RAS/BRAF mutation status, prior radiotherapy, prior surgery, and first-line therapy involving anti-VEGF(R) agents.

Statistical analysis

This study was designed with 80% power to detect an increase in median PFS from 5.1 months (standard second-line therapy) to a target of 7.0 months, using a one-sided type I error rate of 0.025 (Table S1). Accounting for an estimated 5% dropout rate, a total of 98 patients were required. Patient accrual occurred over 24 months, followed by an additional 12 months of follow-up after the last patient enrollment.

Analyses of ORR, DCR were performed in both the intention-to-treat (ITT) population (all enrolled patients who received at least one dose of study treatment) and the efficacy-evaluable population (patients with at least one post-baseline disease assessment), safety analyses were conducted in the ITT population. Time-to-event endpoints (PFS, OS, and DoR) were analyzed using the Kaplan-Meier method. Comparisons between Kaplan-Meier curves were performed using the log-rank test. Hazard ratios (HRs) with associated two-sided 95% confidence intervals (CIs) and P-values were derived from Cox proportional hazards models. ORR and DCR with corresponding 95% CIs were calculated using the Clopper-Pearson method. Subgroup analysis was performed as an exploratory post-hoc analysis. Associations between clinical characteristics and response were assessed using logistic regression; group comparisons for these characteristics were made using Fisher's exact test or the chi-square test, as appropriate. Other clinical outcomes, demographic characteristics, and safety data were summarized descriptively. For time-to-event endpoints, patients who were alive and progression-free at the data cutoff were censored at the date of last tumor assessment. Patients who received subsequent anti-cancer therapy before progression or death were censored at the date of the last disease assessment prior to the start of new therapy. For multivariate Cox regression, variables with a univariate $P < 0.10$ were entered using forward stepwise selection. All primary statistical analyses were conducted using SPSS version 26.0. PSM was subsequently performed using R version 4.2.3.

RESULTS

Demographic characteristics of participants

Between April 28, 2022 and February 29, 2024, 121 patients were screened; 102 met eligibility criteria, were enrolled and received at least one dose of the study regimen (Figure 1). Baseline characteristics of the enrolled patients are

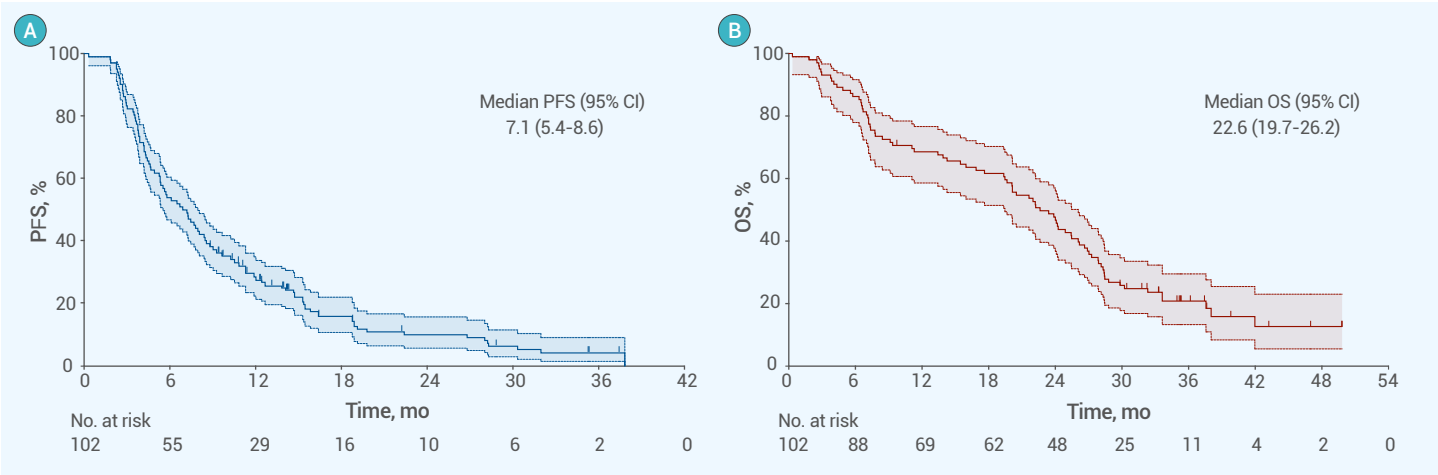


Figure 2. Kaplan-Meier survival curves in study patients (A) PFS. (B) OS. CI, confidence interval; PFS, progression-free survival; OS, overall survival.

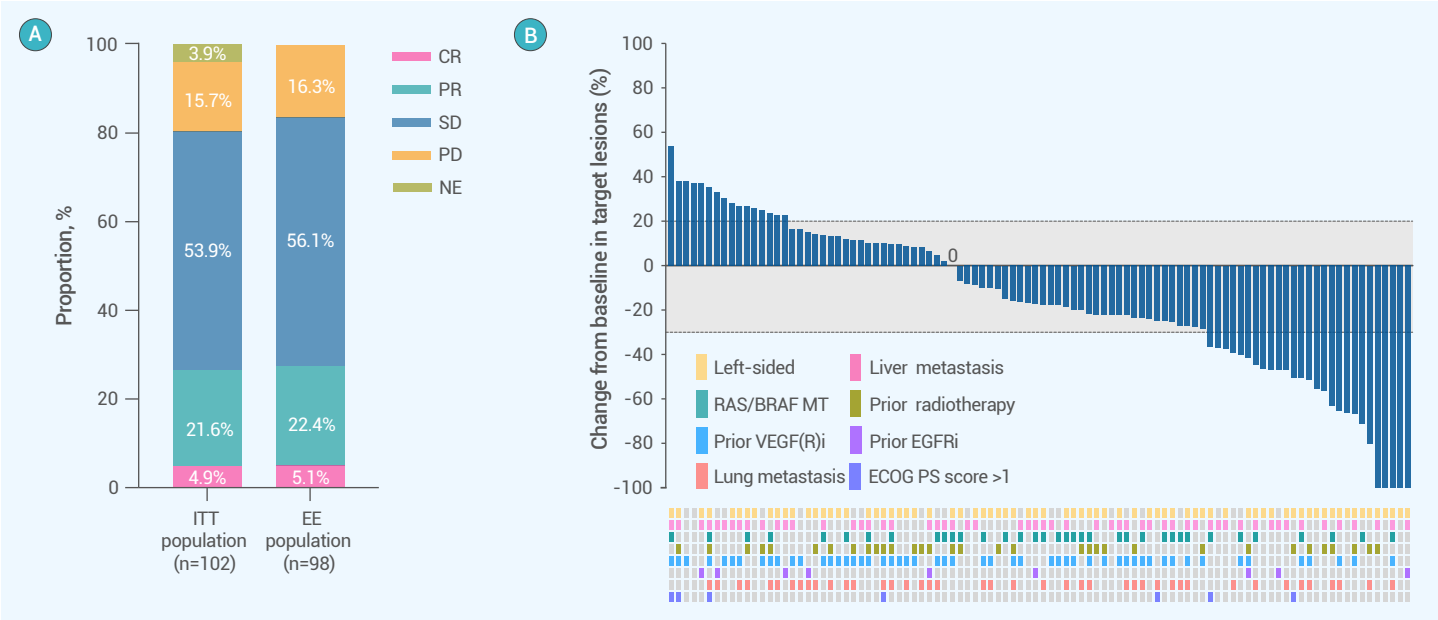


Figure 3. Tumor response in study patients Waterfall plot showing the best percent change in the size of target lesions from baseline. The dashed lines at +20% and -30% indicate thresholds for progressive disease and partial response, respectively, according to RECIST 1.1. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; MT, mutant type; NE, not evaluable; ITT, intention-to-treat; EE, efficacy-evaluable; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRi, epidermal growth factor receptor inhibitor; VEGF(R)i, vascular endothelial growth factor (receptor) inhibitor.

presented in Table 1. The cohort was predominantly male (61.8%), with a median age of 63 years (IQR, 56-71 years). Most patients (93.1%; n=95) had an ECOG PS of 0-1. The primary tumor site was the left colon or rectum in 77.5% (n=79) of patients. Metastatic sites mainly included the liver (56.9%; n=58) and lung (41.2%; n=42). All patients had received first-line systemic chemotherapy, with or without targeted agents, prior to enrollment. Among these prior treatments, 54.9% (n=56) received VEGF(R) inhibitor and 8.8% (n=9) received EGFR inhibitor. Regarding prior local therapies, 86.3% (n=88) had undergone primary tumor resection, and 31.4% (n=32) had received local radiotherapy. Molecular profiling revealed that 36.3% (n=37) had RAS/BRAF mutant tumors. All patients exhibited microsatellite stable (MSS) and/or proficient mismatch repair (pMMR) phenotypes.

Efficacy

As of data cutoff on January 10, 2026, with a median follow-up of 33.2 months (IQR, 25.5-40.0), the median PFS was 7.1 months (95% CI, 5.4-8.6) and median OS was 22.6 months (95% CI, 19.7-26.2) (Figures 2A-B). In the ITT population, the DCR was 80.4% (82 of 102), including 5 (4.9%) confirmed CR, 22 (21.6%) PR and 55 (53.9%) SD, resulting in an ORR of 26.5% (Figure 3A). In the efficacy-evaluable population, the tumor response assessment revealed an ORR of 27.6% (95% CI, 19.2–37.7) and a DCR of 83.7% (95% CI, 74.5-90.1) (Figure 3A). The median DoR was 11.9 months (95% CI, 8.8-15.0). Target lesion size reduction was observed in 60 patients (61.2%) (Figure 3B), with representative cases illustrated in Figures 4A-B.

Univariate analysis demonstrated significant survival differences based on certain specific clinical factors (Figure S1). Patients with prior surgical resection of the primary tumor exhibited improved median PFS (7.4 vs. 3.6 months; HR, 0.50; 95% CI, 0.28-0.89; P = 0.017) and OS (24.0 vs. 13.4 months; HR, 0.49; 95% CI, 0.27-0.90; P = 0.018) compared to those without resection (Figures S2A-B). Similarly, patients without liver metastasis had significantly longer median PFS (9.2 vs. 5.6 months; HR, 0.64; 95% CI, 0.42-0.97; P = 0.032) and OS (26.9 vs. 15.7 months; HR, 0.62; 95% CI, 0.40-0.97; P = 0.033) than those with liver metastasis (Figures S2C-D). Patients with a history of prior VEGF(R) inhibitor also showed poor median PFS (5.6 vs. 8.2 months; HR, 1.79; 95% CI, 1.17-2.74; P = 0.007) and OS (20.1 vs. 27.4 months; HR, 1.81; 95% CI, 1.16-2.82; P = 0.008) (Figures S2E-F). Multivariate analysis further confirmed that primary tumor resection, liver metastasis, and prior anti-VEGF(R) therapy were independent prognostic factors for both PFS and OS (Table S2). Some of these survival outcomes were subsequently validated in a real-world control cohort (Table S3, Figures S3-S4).

Furthermore, building on our prior research and Guo's study, we evaluated two fruquintinib dosing regimens.[16,22] Among 67 patients receiving the stan-

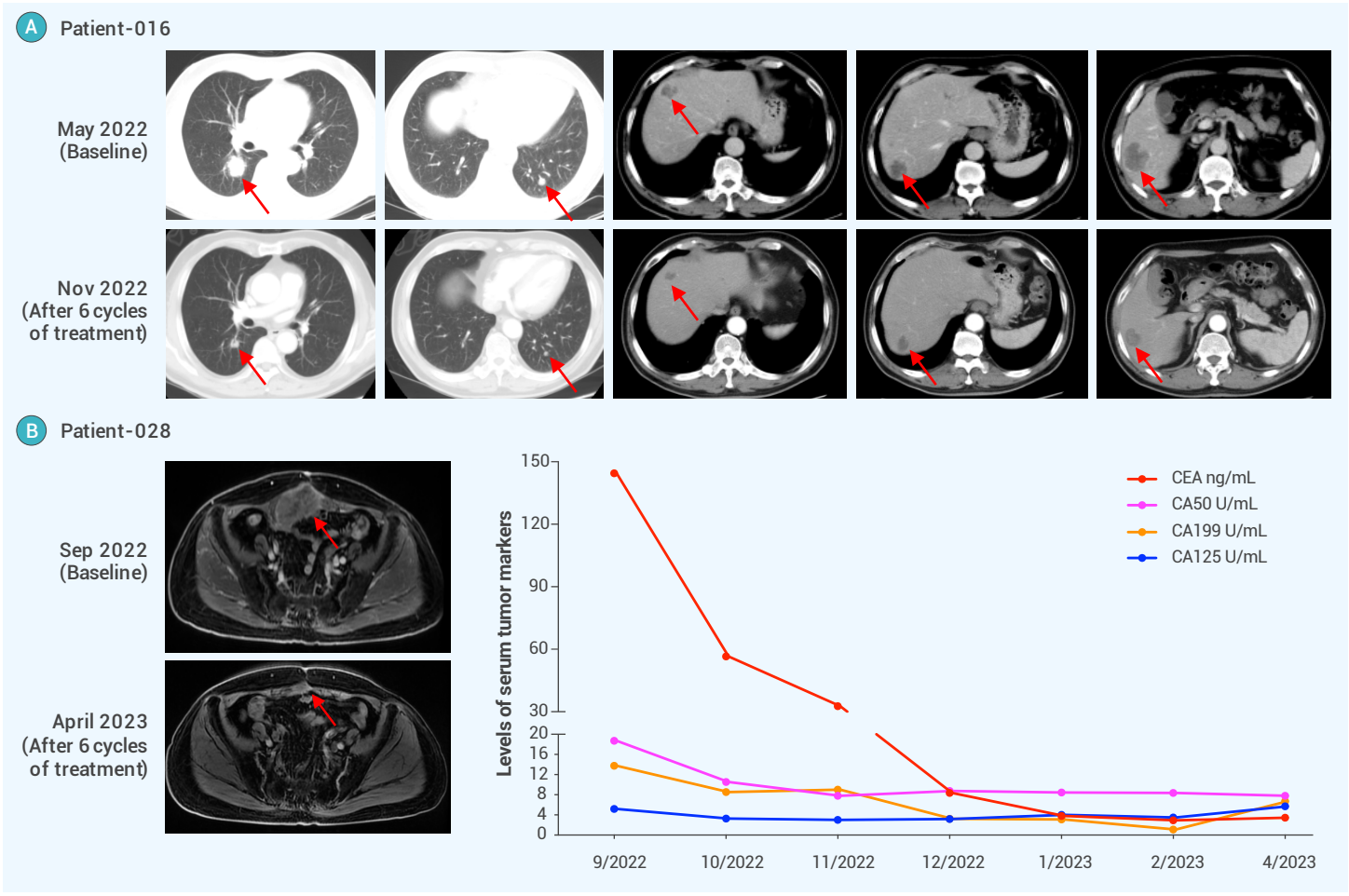


Figure 4. Typical cases presentation Representative images of two patients and the dynamic changes of serum tumor markers. CA199, carbohydrate antigen 199; CA50, carbohydrate antigen 50; CA125, carbohydrate antigen 125; CEA, carcinoembryonic antigen.

dard 4-week regimen, median PFS was 6.5 months (95% CI, 5.3-8.8) (Figure S5). In contrast, 35 patients receiving an adjusted 3-week regimen achieved a median PFS of 7.3 months (95% CI, 4.5-14.7). Overall, the result of the adjusted 3-week regimen was not inferior to that of the standard 4-week regimen (HR, 0.74; 95% CI, 0.48-1.14; P = 0.172), supporting the clinical feasibility of flexible dosing strategies.

Subgroup analysis

Subgroup analysis was used to identify the characteristics of potential benefit population. To compare with mCRC patients who are currently receiving or have already received second-line systemic therapy in the real world, we screened 263 eligible patients from 916 CRC patients in our centers as the control group (Figure 1, Tables S3-S4).

The forest plot after adjusting for covariates (including age, sex, liver metastasis, prior surgery, and prior anti-VEGF(R) therapy) indicated that patients in the following subgroups were more likely to achieve PFS improvement from the study protocol: those aged ≤ 60 years (adjusted HR, 0.60; 95% CI, 0.43-0.85; P = 0.004), male (adjusted HR, 0.63; 95% CI, 0.47-0.86; P = 0.003), with previous surgery (adjusted HR, 0.61, 95% CI, 0.47-0.80; P < 0.001), without liver metastasis (adjusted HR, 0.49; 95% CI, 0.34-0.72; P < 0.001), and without prior anti-EGFR (adjusted HR, 0.65; 95% CI, 0.50-0.84; P = 0.001) or anti-VEGF(R) (adjusted HR, 0.57; 95% CI, 0.40-0.81; P = 0.002) targeted therapy (Figure 5). This benefit was observed regardless of primary tumor location, presence or absence of lung metastasis, prior history of radiotherapy, or RAS/BRAF mutation status.

Safety

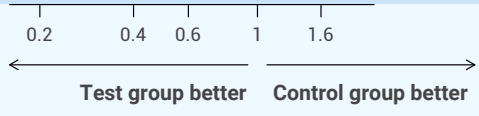
No new safety concerns were detected. Most patients (91.2%) experienced at least one AE and the majority were grade 1 or 2 (Table 2). The most common AEs were neutropenia (57.8%), nausea and/or vomiting (50.0%) and leukopenia (47.1%). Grade 3 or 4 AEs were observed in 38.2% patients, mainly including neutropenia (11.8%), leukopenia (5.9%) and hand-foot syndrome (3.9%). No treatment-related deaths occurred. Fruquintinib dose reductions occurred in 21 patients (20.6%); most common reasons were hand-foot syndrome (n=9), proteinuria (n=5), and hypertension (n=4). Treatment interruption (≥ 7 days) occurred in 19 patients (18.6%), and permanent discontinuation due to AEs in 3 patients (2.9%). Patients who developed COVID-19 were managed according to local guidelines; fruquintinib and chemotherapy were temporarily withheld until resolution of acute symptoms. As of January 10, 2026, 43 patients had completed the study treatment protocol and 5 continued on fruquintinib maintenance therapy without disease progression.

PSM analysis

Following PSM, 78 patients from the test group (n=102 screened) were matched with 130 patients from the control group (n=263 screened) (Figures 6A-B, Table S5). The test group demonstrated significantly improved median PFS compared to the control group (6.6 vs. 5.3 months; HR, 0.68; 95% CI, 0.51-0.91; P = 0.010) (Figure 6C). Corresponding increases were observed in the ORR (23.1% vs. 16.9%; OR, 1.47; 95% CI, 0.74-2.96; P = 0.280) and DCR (79.5% vs. 67.7%; OR, 1.85; 95% CI, 0.98-3.50; P = 0.079), although these differences did not reach statistical significance (Table S6). Median OS was also longer in the test group (23.0 vs. 19.7 months), but this difference was also not statistically significant (HR, 0.93; 95% CI, 0.68-1.27; P = 0.640) (Figure 6D).

In terms of safety, the test group reported a lower incidence of grade ≥ 3 AEs (35.9% vs. 60.8%; Table S7). Specifically, the fruquintinib-based regimen was associated with reduced rates of grade 3/4 hematological events, gastrointestinal emergencies, and infusion/allergic reactions compared to the control regimen.

Subgroup	Control group*	Test group*	Adjusted HR (95% CI)**	P
Overall	263/263	97/102	0.66 (0.52, 0.84)	0.001
Age, year				
>60	114/114	52/55	0.73 (0.52, 1.03)	0.076
≤60	149/149	45/47	0.60 (0.43, 0.85)	0.004
Sex				
Male	173/173	59/63	0.63 (0.47, 0.86)	0.003
Female	90/90	38/39	0.69 (0.45, 1.03)	0.071
ECOG PS score				
0-1	247/247	90/95	0.66 (0.51, 0.84)	0.001
2	16/16	7/7	0.48 (0.16, 1.44)	0.191
Primary tumor location				
Left-sided	199/199	77/79	0.69 (0.52, 0.91)	0.009
Right-sided	64/64	20/23	0.46 (0.26, 0.80)	0.006
Liver metastasis				
Yes	160/160	56/58	0.81 (0.59, 1.11)	0.196
No	103/103	41/44	0.49 (0.34, 0.72)	<0.001
Lung metastasis				
Yes	124/124	41/42	0.64 (0.44, 0.93)	0.020
No	139/139	56/60	0.69 (0.50, 0.97)	0.032
Prior surgery				
Yes	201/201	83/88	0.61 (0.47, 0.80)	<0.001
No	62/62	14/14	0.90 (0.47, 1.72)	0.743
Prior radiotherapy				
Yes	63/63	31/32	0.61 (0.38, 0.98)	0.042
No	200/200	66/70	0.67 (0.50, 0.89)	0.007
Prior anti-EGFR therapy				
Yes	39/39	9/9	1.05 (0.47, 2.37)	0.903
No	224/224	88/93	0.65 (0.50, 0.84)	0.001
Prior anti-VEGF(R) therapy				
Yes	112/112	54/56	0.80 (0.57, 1.12)	0.188
No	151/151	43/46	0.57 (0.40, 0.81)	0.002
RAS/BRAF status				
Mutant type	91/91	35/37	0.60 (0.40, 0.90)	0.013
Wild type	91/91	41/43	0.39 (0.26, 0.60)	<0.001
Unknown	81/81	21/22	1.40 (0.85, 2.31)	0.185



*no. of events/total no.

**adjusted for age, sex, liver metastasis, prior surgery, and prior anti-VEGF(R) therapy

Figure 5. Subgroup analysis of PFS between the two groups before PSM CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; PSM, propensity score matching; ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF(R), vascular endothelial growth factor (receptor).

DISCUSSION

To our knowledge, this trial represents the first evaluation of fruquintinib, an anti-angiogenic small-molecule kinase inhibitor, combined with chemotherapy as a second-line treatment for mCRC. The results demonstrate promising antitumor activity alongside a significantly reduced incidence of AEs.

For patients with microsatellite-stable mCRC lacking low-frequency or rare

Table 2. Treatment-related adverse events (N = 102).

Adverse events, No. (%)	Any grade	Grade ≥ 3
Any	93 (91.2)	39 (38.2)
Leukopenia	48 (47.1)	6 (5.9)
Neutropenia	59 (57.8)	12 (11.8)
Thrombocytopenia	28 (27.5)	3 (2.9)
Anemia	41 (40.2)	2 (2.0)
Lymphocytopenia	46 (45.1)	0
Nausea and/or vomiting	51 (50.0)	0
Fatigue	39 (38.2)	0
Decreased appetite	33 (32.4)	0
Abnormal liver test results	19 (18.6)	2 (2.0)
Abdominal pain	20 (19.6)	0
Diarrhea	34 (33.3)	2 (2.0)
Electrolyte disturbance	29 (28.4)	3 (2.9)
Bleeding or haemorrhage	11 (10.8)	0
Gastrointestinal perforation	1 (1.0)	1 (1.0)
Subileus	3 (2.9)	0
Thromboembolic event	3 (2.9)	2 (2.0)
Proteinuria	32 (31.4)	2 (2.0)
Hypertension	23 (22.5)	1 (1.0)
Hyperglycemia	4 (3.9)	0
Hypothyroidism	19 (18.6)	0
Rash	18 (17.6)	1 (1.0)
Hand-foot syndrome	40 (39.2)	4 (3.9)
Hoarseness	15 (14.7)	0
Mucositis[a]	28 (27.5)	1 (1.0)
Pneumonitis[b]	7 (6.9)	3 (2.9)
Neurotoxicity	10 (9.8)	0
Infusion-related reaction	2 (2.0)	0

[a]Mucositis includes events of stomatitis, oral mucositis, and oral inflammation.

[b]Pneumonitis includes events of lung infection and COVID-19.

gene alterations, fluorouracil/irinotecan/oxaliplatin-based chemotherapy remains the cornerstone.[23] While adding molecular targeted agents (anti-VEGF(R) or anti-EGFR monoclonal antibodies) to first- and second-line chemotherapy improves efficacy, the median PFS with second-line targeted therapy has only doubled from a historical baseline of 3 months, and this benefit comes with a high burden of grade ≥ 3 AEs (50-80%).[10,11,24-27] Furthermore, socioeconomic factors in China create a substantial demand for alternatives to infusional VEGF/EGFR monoclonal antibodies.

Unlike the multi-kinase inhibitor regorafenib, fruquintinib is a highly selective inhibitor of VEGFR-1, -2, and -3, approved worldwide for third-line mCRC treatment.[13,14] The STREAM study, exploring regorafenib monotherapy as second-line treatment for RAS-mutant mCRC, reported an ORR of 10.9%, DCR of 54.6%, median PFS of 3.6 months, median OS of 18.9 months, and grade ≥ 3 AEs in 39.1% of patients.[28] Preclinical studies suggest a synergistic anti-tumor effect and biological safety when fruquintinib is combined with chemotherapy, a strategy also yielding encouraging results in advanced gastric cancer settings.[18,29]

In this trial, enrolling mCRC patients progressing after first-line systemic therapy, the combination of fruquintinib with chemotherapy improved clinical outcomes. We observed an improved median PFS (6.6 vs. 5.3 months; P = 0.010), median OS (23.0 vs. 19.7 months; P = 0.640), ORR (23.1% vs. 16.9%), and DCR (79.5% vs. 67.7%). The 1.3-month PFS improvement is clinically meaningful, comparable to the gains achieved by continuing or reintroducing bevacizumab with second-line chemotherapy in the ML18147 (PFS: 5.7 vs. 4.1 months) and BEBYP (PFS: 6.8 vs. 5.0 months) trials.[8,9] Although the OS benefit did not reach statistical significance, the 3.3-month directional prolongation is notable, as maximal OS gains are typically seen with first-line therapy. In comparison to other second-line VEGF-pathway targeting strategies, the efficacy observed in our study is comparable to that reported in the RAISE trial (ramucirumab + FOLFIRI: median PFS 5.7 months, grade ≥ 3 AEs 79%) and the VELOUR trial (aflibercept + FOLFIRI: median PFS 6.9 months, grade ≥ 3 AEs 83.5%).[10,11] Our fruquintinib plus chemotherapy regimen achieved a median PFS of 6.6 months, OS of 23.0 months, and a significantly lower incidence of grade ≥ 3 AEs (35.9%), suggesting a potentially more

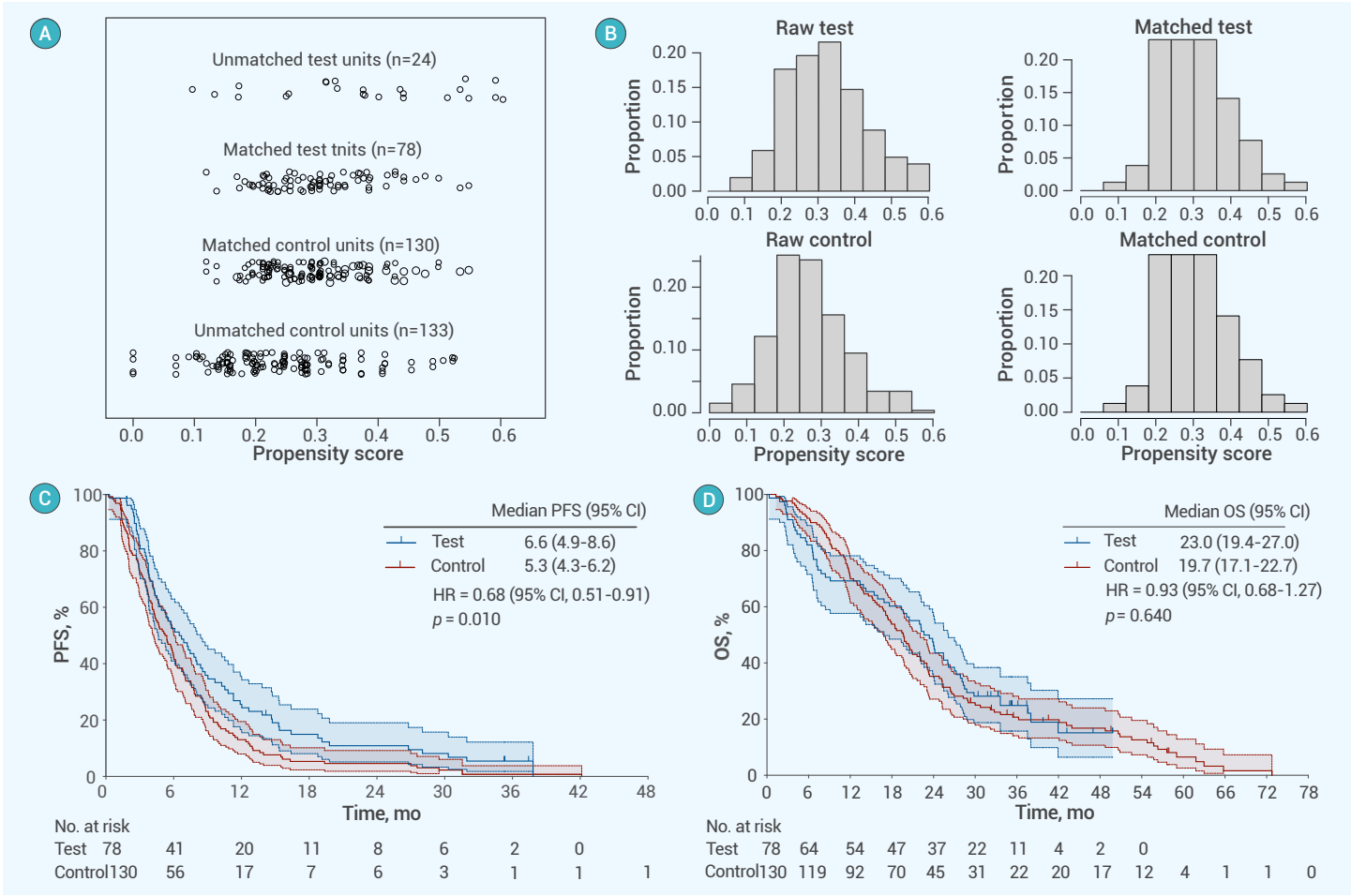


Figure 6. PSM and survival curves of matched patients after PSM (A) Distribution of patients before and after propensity score matching. (B) Data distribution before and after propensity score matching. (C) PFS. (D) OS. CI, confidence interval; HR, hazard ratio; PFS, progression-free survival; PSM, propensity score matching; OS, overall survival.

favorable toxicity profile while maintaining comparable or improved efficacy.

The safety profiles of both fruquintinib and chemotherapy were consistent with previous reports, with no new safety signals identified. Most AEs were grade 1-2 and manageable with standard interventions. Crucially, the incidence of grade ≥ 3 AEs was significantly lower with fruquintinib plus chemotherapy (35.9%) compared to the control group (60.8%), with fewer instances of clinically relevant myelosuppression, gastrointestinal toxicities, and infusion reactions. Three patients (2.9%) without disease progression developed fatal grade 3 pneumonitis during the study period; all were infected with COVID-19, and their deaths were attributed to COVID-19 complications. Unlike intravenous biologics such as bevacizumab, fruquintinib is conveniently administered at home without infusion-related costs or hospital visits. Moreover, since its inclusion in the National Reimbursement Drug List in China, the out-of-pocket cost of fruquintinib has been substantially reduced, making it a more economically viable option for many mCRC patients. These socioeconomic advantages, combined with its favorable safety profile, further support fruquintinib plus chemotherapy as a practical and equitable second-line treatment option for mCRC.

Fruquintinib has demonstrated efficacy combined with cytotoxic agents in gastrointestinal cancers, as supported by the randomized phase 3 FRUTIGA trial a Phase III study in advanced gastric cancer and validated here.[30] This compatibility may stem from fruquintinib's high kinase selectivity compared to earlier VEGFR inhibitors, ensuring strong target exposure within the tumor microenvironment. This promotes sustained inhibition of angiogenesis and durable anti-tumor activity. Additionally, fruquintinib has been shown to induce an early CEA response.[31] Bai et al found that mCRC patients treated with fruquintinib obtained an improved median OS (12.8 vs. 7.8 months; HR, 0.45; P < 0.001) and median PFS (5.6 vs. 3.7 months; HR, 0.49; P < 0.001) if an early CEA response (≥ 50% decrease from baseline) was confirmed.[32] We observed this response in a subset of our patients, warranting further biomarker validation.

This present trial has several limitations. First, it was an open-label, phase II study with a relatively small sample size. Second, as a domestic multicenter study conducted solely in Central China, the results may lack generalizability to other populations. Third, the absence of a randomized control arm is a constraint, although PSM analysis was performed against a real-world cohort; however, such comparisons carry inherent risks of bias. Fourth, the follow-up duration was relatively short, and longer observation is needed to confirm the durability of survival benefits and to capture late-onset AEs.

In conclusion, our findings provide the first evidence that combining fruquintinib with chemotherapy, followed by fruquintinib maintenance, is clinically feasible as a second-line treatment for mCRC, this regimen demonstrated acceptable tolerability and promising efficacy. It represents a viable alternative treatment strategy deserving further evaluation in randomized controlled trials.

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AUTHOR CONTRIBUTIONS

Y.C. performed study conception and design. All authors enrolled patients and collected data. Y.C. and L.Y. conducted quality control and supervision. W.Z. and J.L. did the statistical analysis and drafted the manuscript. All authors had full access to all the data in the study and accept the responsibility to submit it for publication. All authors read and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

ETHICAL STATEMENT AND PATIENT CONSENT

The study was approved by the independent ethics committee/institutional review board of Renmin Hospital of Wuhan University and each participating center (Approval No.: WDRY2021-K036) and registered for clinical trials (Chictr.org.cn Identifier: ChiCTR2200059280), the registration date was March 20, 2022, and the study planned duration was from April 13, 2022 to April 13, 2024. Written informed consent was obtained from all participants.

DATA AND CODE AVAILABILITY

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

SUPPLEMENTAL INFORMATION

It can be found online at https://doi.org/10.59717/j.xinn-oncol.2026.100026