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Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer
The FRESCO Randomized Clinical Trial

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IMPORTANCE Patients with metastatic colorectal cancer (CRC) have limited effective and tolerable treatment options.

OBJECTIVE To evaluate the efficacy and safety of oral fruquintinib, a vascular endothelial growth factor receptor (VEGFR) inhibitor, as third-line or later therapy in patients with metastatic CRC.

DESIGN, SETTING, AND PARTICIPANTS FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) was a randomized, double-blind, placebo-controlled, multicenter (28 hospitals in China), phase 3 clinical trial. From December 2014 to May 2016, screening took place among 519 patients aged 18 to 75 years who had metastatic CRC that progressed after at least 2 lines of chemotherapy but had not received VEGFR inhibitor therapy; 416 met the eligibility criteria and were stratified by prior anti-VEGF therapy and K-*ras* status. The final date of follow-up was January 17, 2017.

INTERVENTIONS Patients were randomized in a 2:1 ratio to receive either fruquintinib, 5 mg (n = 278) or placebo (n = 138) orally, once daily for 21 days, followed by 7 days off in 28-day cycles, until disease progression, intolerable toxicity, or study withdrawal.

MAIN OUTCOMES AND MEASURES The primary end point was overall survival. Key secondary efficacy endpoints were progression-free survival (time from randomization to disease progression or death), objective response rate (confirmed complete or partial response), and disease control rate (complete or partial response, or stable disease recorded ≥8 weeks postrandomization). Duration of response was also assessed. Safety outcomes included treatment-emergent adverse events.

RESULTS Of the 416 randomized patients (mean age, 54.6 years; 161 [38.7%] women), 404 (97.1%) completed the trial. Median overall survival was significantly prolonged with fruquintinib compared with placebo (9.3 months [95% CI, 8.2-10.5] vs 6.6 months [95% CI, 5.9-8.1]); hazard ratio (HR) for death, 0.65 (95% CI, 0.51-0.83; $P < .001$). Median progression-free survival was also significantly increased with fruquintinib (3.7 months [95% CI, 3.7-4.6] vs 1.8 months [95% CI, 1.8-1.8] months); HR for progression or death, 0.26 (95% CI, 0.21 to 0.34; $P < .001$). Grades 3 and 4 treatment-emergent adverse events occurred in 61.2% (170) of patients who received fruquintinib and 19.7% (27) who received placebo. Serious adverse events were reported by 15.5% (43) of patients in the fruquintinib group and 5.8% (8) in the placebo group, with 14.4% (40) of fruquintinib-treated and 5.1% (7) of placebo-treated patients requiring hospitalization.

CONCLUSIONS AND RELEVANCE Among Chinese patients with metastatic CRC who had tumor progression following at least 2 prior chemotherapy regimens, oral fruquintinib compared with placebo resulted in a statistically significant increase in overall survival. Further research is needed to assess efficacy outside of China.

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Colorectal cancer (CRC) is the third most common cancer worldwide, causing more than 800 000 deaths in 2015.[1] The annual incidence and mortality of CRC in China has increased steadily since 2000, with 376 300 new cases and 191 000 deaths reported in 2015.[2]

Fluorouracil with leucovorin plus either irinotecan[3] or oxaliplatin[4] are the standard chemotherapeutic regimens for treating metastatic CRC.[5,6] To improve patient outcomes, chemotherapy can be combined with bevacizumab[7,8] or aflibercept[8] to target the vascular endothelial growth factor (VEGF) pathway or with cetuximab or panitumumab to target the epidermal growth factor receptor (EGFR).[9,10] Although patients who progress after receiving 2 lines of systemic chemotherapy may still have good performance status, third-line treatment options are limited. There is therefore a strong unmet clinical need for treatment options in the third-line setting for metastatic CRC, especially in China.

The VEGF pathway is vital to the neoangiogenesis associated with tumor proliferation.[11] Antiangiogenic agents targeting the VEGF pathway include those that inhibit the ligand (ie, VEGF inhibitors) or its receptor (ie, vascular endothelial growth factor receptor [VEGFR] inhibitors). These agents inhibit new blood vessel growth and lead to vascular regression, tumor vessel normalization, and constriction; offsetting chemotherapy's induction of VEGF.[11] The rationale of continuing to target the VEGF pathway in metastatic CRC was confirmed when third-line monotherapy with the VEGFR inhibitor regorafenib improved survival in global[12] and Asian[13] study populations. However, the efficacy of regorafenib is limited and its adverse effects, particularly hepatotoxicity and fatigue, may be difficult to manage.[12]

Fruquintinib is a VEGFR inhibitor that blocks new blood vessel growth associated with tumor proliferation.[14] It is a potent, highly selective small-molecule inhibitor of VEGFR-1, -2, and -3.[15] This phase 3 study was conducted to assess its efficacy and adverse event profile in patients with metastatic CRC that had progressed after second-line or subsequent treatment.

Key Points

Question Does fruquintinib prolong overall survival in patients with metastatic colorectal cancer (CRC) who have tumor progression following at least 2 lines of chemotherapy, targeted treatment, or both?

Findings In this randomized clinical trial involving 416 patients in China with metastatic CRC who had tumor progression following at least 2 lines of chemotherapy, treatment with fruquintinib resulted in a statistically significant increase in overall survival compared with placebo (median survival time, 9.3 vs 6.6 months).

Meaning Fruquintinib may prolong survival in patients with metastatic colorectal cancer who had tumor progression after previous treatment, although the efficacy of this therapy remains to be assessed outside of China.

Methods

The study protocol (Supplement 1) was approved by the independent ethics committee/institutional review board of each participating center. This study was conducted in accordance with the Declaration of Helsinki[16] and Guidelines for Good Clinical Practice, as well as the local laws and regulations of China. An independent data monitoring committee, comprising 3 oncologists and 1 statistician, ensured the overall integrity of the trial and safety of the participants.

Patient Eligibility

Eligible patients were aged 18 to 75 years, weighed at least 40 kg, and had to provide written informed consent prior to enrollment. They had to have histologically and/or cytologically confirmed metastatic CRC that progressed following at least 2 standard chemotherapy regimens. Patients had to have evidence of disease progression during or within 3 months after the last administration of standard treatment or to have stopped treatment because of unacceptable toxic effects.

Other eligibility criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1; left ventricular ejection fraction of 50% or greater; measurable disease by Response Evaluation Criteria in Solid Tumors version 1.1; adequate bone marrow, liver, and renal function; and a life expectancy of at least 12 weeks.

Prior treatment with VEGF inhibitors (eg, bevacizumab and aflibercept) or EGFR inhibitors was permitted and was used as one of the stratification factors in efficacy analysis. However, because fruquintinib is a VEGFR inhibitor, patients who received prior treatment with other VEGFR inhibitors (eg, sorafenib, sunitinib, axitinib, regorafenib, ramucirumab, apatinib, axitinib, famitinib, or other tyrosine kinase inhibitors) were excluded. Full inclusion and exclusion criteria are listed in eTable 1 in Supplement 2.

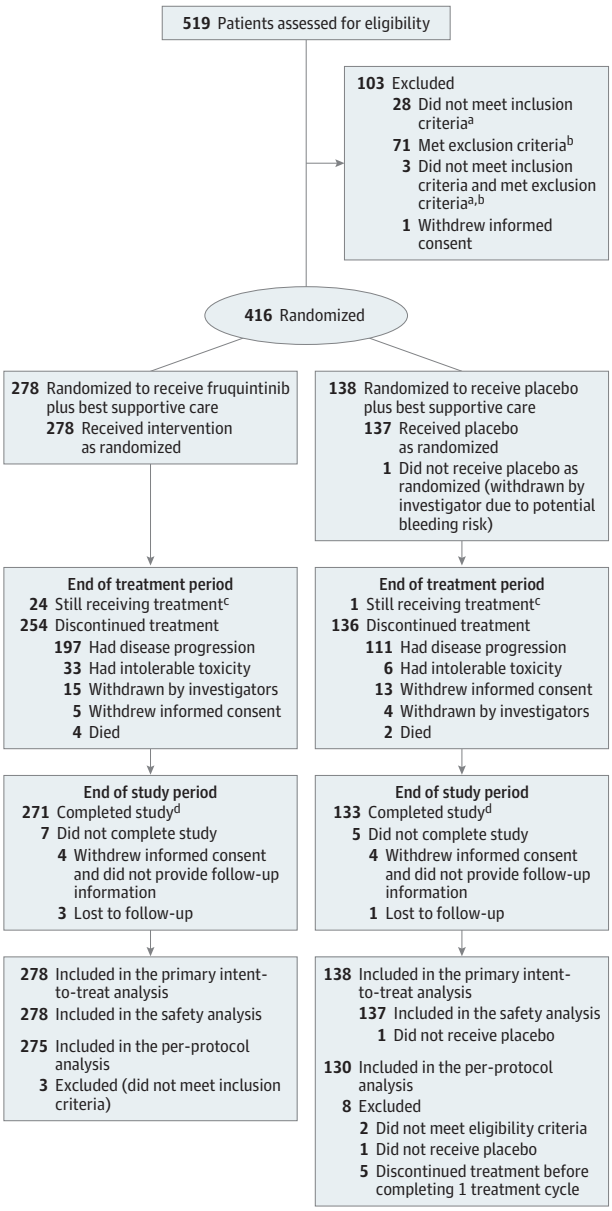
Study Design and Treatment

FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial in patients with metastatic CRC who had tumor progression following treatment regimens that included fluoropyrimidine, oxaliplatin, and irinotecan.

Patients were randomly assigned by an interactive web response system in a 2:1 ratio to receive either oral fruquintinib (5 mg/d) or matching placebo, both in combination with best supportive care (**Figure 1**). Randomization was stratified by prior use of VEGF inhibitor treatment (yes vs no) and K-*ras* mutational status (wild type vs mutated). The investigators, sponsor, and patients were blinded to treatment allocation until database lock (sponsor) or study completion (investigators).

Eligible participants repeated the 28-day treatment cycle of 3 weeks on followed by 1 week off until disease progression, death, unacceptable toxicity, withdrawal of consent by the patient, or discontinuation by the physician. All patients received best supportive care excluding other investigational antitumor agents or anticancer treatments during the study period (from 28 days before the informed consent form date

Figure 1. Flow of Patients With Metastatic Colorectal Cancer Receiving Fruquintinib vs Placebo



[a] Inclusion criteria are detailed in eTable 1 in Supplement 2.

[b] More detailed information regarding the 71 patients who met the exclusion criteria is provided in eTable 6 in Supplement 2.

[c] Indicates patients who met the end of treatment criteria but were still receiving the study treatment at the cutoff date (January 17, 2017).

[d] Includes patients who died or were still alive at the study cutoff date.

to end of treatment). Protocol-predefined dose reduction (in two 1-mg/d increments) was permitted to manage clinically significant treatment-related toxic effects (eTable 2 in Supplement 2). Treatment was discontinued permanently if the toxicity did not resolve after a 2-week treatment interruption or did not meet protocol-defined criteria after 2 dose reductions. No crossover between treatment groups was permitted.

Clinical Assessments, Outcomes, and End Points

The primary efficacy outcome was overall survival, defined as the time from randomization until death. For patients who were not reported to have died at the planned analysis cutoff, the final known date of survival was used as the censoring date.

Tumor assessment was performed every 8 weeks as defined by Response Evaluation Criteria in Solid Tumors version 1.1. Key secondary efficacy end points were progression-free survival (defined as time from randomization to disease progression or death), objective response rate (defined as a confirmed complete or partial response), and disease control rate (defined as a complete or partial response, or stable disease recorded ≥8 weeks after randomization). Duration of response was also assessed.

Safety assessments included adverse events, laboratory abnormalities (hematology, clinical chemistry, and urinalysis), vital signs, electrocardiograms, and echocardiographs. Treatment-emergent adverse events were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. The duration, severity, and relation to study medication, based on the investigator's clinical assessment, were recorded at scheduled study visits.

Statistical Methods

Taking into consideration the previous phase 1b and phase 2 efficacy data for fruquintinib,[17] assuming the hazard ratio (HR) for death with fruquintinib over placebo was 0.7, this would correspond to a median overall survival of 9.0 months for fruquintinib and 6.3 months for placebo. Based on this assumption, it was calculated that 280 overall survival events would provide an 80% power to detect a difference in overall survival between the 2 treatment groups, with a 2-sided P value of .05 indicating statistical significance. To achieve this, the study was planned to randomize approximately 400 patients.

Statistical analyses were carried out using SAS version 9.2. The statistical analysis plan and tests for the proportional hazards assumption are detailed in Supplement 3 and Supplement 4. Overall survival and progression-free survival were compared using a stratified log-rank test. Hazard ratios with 95% CIs were estimated using the Cox model, adjusting for baseline stratification factors. To evaluate the effect of the different study sites, post hoc analyses of overall survival and progression-free survival were performed using stratified Cox models with site as a random effect. Kaplan-Meier curves and median survival were estimated for each treatment group. The Mantel-Haenszel test was used for comparisons of objective response rate and disease control rate. Subgroup analyses of overall survival and progression-free survival were conducted for the covariates using descriptive statistics and HR (95% CI). Post hoc tests for interaction of treatment by each covariate were performed by fitting Cox models, including treatment, covariate, and covariate by treatment interaction term. The significance level for the interaction test was set at 2-sided $P = .05$.

The assumption of proportionality was assessed first by examining plots of complementary log-log (event times) vs log (time), and if this raised concerns, by adding interaction of treatment with time to the stratified Cox model to assess the

extent to which this represented random variation. If a lack of proportionality was evident, the variation in treatment effect would be described by presenting a piecewise HR calculated over distinct time periods from a post hoc analysis. In such circumstances, the HR can still be meaningfully interpreted as an average HR over time.[18,19]

The efficacy analyses were based on the intention-to-treat population, which included all randomized patients. The per-protocol set included the patients who did not experience any major protocol deviations that may have influenced the overall survival evaluation and who completed at least 1 treatment cycle. The per-protocol set was only analyzed for overall survival. The safety analysis set included all randomized patients who received at least 1 dose of study treatment. Missing efficacy data were not imputed when performing statistical analyses.

Results

Patients

Between December 8, 2014, and May 13, 2016, 519 patients from 28 study sites in China were screened; the 416 eligible patients who consented to participate were randomized to receive fruquintinib (n = 278) or placebo (n = 138) plus best supportive care (for both groups) and were included in the intention-to-treat population. Except for 1 patient in the placebo group, all patients received treatment as allocated and were included in the safety analysis. Participant flow through the study is shown in Figure 1. The median follow-up time was 13.3 months for the fruquintinib group and 13.2 months for the placebo group. The final date of follow-up was January 17, 2017.

Patient baseline characteristics are summarized in **Table 1**. Of the 416 randomized patients (mean age, 54.6 years; 161 [38.7%] women), 404 (97.1%) completed the trial. Most baseline demographics, disease characteristics, and prior treatments were similar between the treatment groups, except the proportion of men was higher in the placebo group than in the fruquintinib group. Most patients had multiple metastases, with liver metastases present in 185 of 278 (66.5%) in the fruquintinib group and in 102 of 138 (73.9%) in the placebo group. Between-group proportions were similar for patients who had previously received VEGF inhibitors (30.2% [84] in the fruquintinib group vs 29.7% [41] in the placebo group) or EGRF inhibitors (14.4% [40] in the fruquintinib group vs 13.8% [19] in the placebo group), and who had K-*ras* mutations (43.5% [121] in the fruquintinib group vs 46.4% [64] in the placebo group).

After disease progression or the end of study treatment, 188 patients (45.2%) received further systemic treatment (118 of 278 [42.4%] in the fruquintinib group and 70 of 138 [50.7%] in the placebo group), which included cytotoxic anticancer therapies, monoclonal antibodies, and kinase inhibitors (eTable 3 in Supplement 2).

Efficacy

At the planned cutoff date (January 17, 2017), after 297 deaths, the median overall survival was 9.30 (95% CI, 8.18-10.45) months in the fruquintinib group and 6.57 (95% CI, 5.88-8.11) months in the placebo group (HR for death, 0.65 [95% CI, 0.51-0.83]; log-rank test $P < .001$; **Figure 2**A). The overall survival findings in the per-protocol set were similar: 9.30 (95% CI, 8.18-10.45) months with fruquintinib and 6.80 (95% CI, 5.91-8.38) months with placebo (HR for death, 0.66 [95% CI, 0.52-0.85]; log-rank test $P = .001$). Sensitivity analyses of the overall survival data considering the effect of study site showed similar results, with HRs for death of 0.63 (95% CI, 0.49-0.81) in the intention-to-treat population and 0.65 (95% CI, 0.50-0.83) in the per-protocol set (eTable 4 in Supplement 2).

Median progression-free survival was also significantly increased with fruquintinib (3.71 [95% CI, 3.65-4.63] vs 1.84 [95% CI, 1.81-1.84] months with placebo; HR for progression or death, 0.26 [95% CI, 0.21-0.34]; $P < .001$; Figure 2B). Sensitivity analysis of progression-free survival considering site effect provided similar results (3.7 [95% CI, 3.7-4.6] months with fruquintinib vs 1.8 [95% CI, 1.8-1.8] months with placebo; HR for progression or death, 0.26 [95% CI, 0.20-0.33]; eTable 4 in Supplement 2). Given that the assumption of proportional hazards for the Cox model was violated, the piecewise HRs for progression-free survival were explored. The results showed a superior treatment effect of fruquintinib compared with placebo during both time intervals (HR for progression or death, 0.20 [95% CI, 0.14-0.29] during the interval from 0 to 1.85 months postrandomization; HR for progression or death, 0.12 [95% CI, 0.05-0.26] during the interval from 1.85 months postrandomization and thereafter). The cutoff point of 1.85 months postrandomization was the time point at which the 2 progression-free survival curves approached each other most closely.

Subgroup analyses of overall survival were generally consistent with benefit in the intention-to-treat population across nearly all subgroups (**Figure 3**). The overall survival benefit among the patients who had previously been treated with VEGF inhibitors (84 with fruquintinib and 41 with placebo) was similar to that in the intention-to-treat population, with an HR of 0.68 (95% CI, 0.45-1.03). Subgroup analyses revealed no significant difference between fruquintinib and placebo among women (HR for death, 0.85 [95% CI, 0.57-1.29]), patients aged 65 years and older (HR for death, 0.95 [95% CI, 0.55-1.63]), or among patients with right-sided primary tumors (HR for death, 0.96 [95% CI, 0.53-1.75]). Progression-free survival was superior for fruquintinib compared with placebo across all patient subgroups. The test for interaction of treatment by K-*ras* status was statistically significant ($P = .04$; see **Figure 4**), although the small patient numbers in each subgroup precluded firm conclusions.

Compared with placebo, patients treated with fruquintinib also demonstrated a significantly higher objective response rate (13 of 278 patients [4.7%] vs 0%; $P = .01$; treatment difference, 4.7% [95% CI, 2.1%-7.2%]) and disease control rate (62.2% vs 12.3%; $P < .001$; treatment difference, 49.9% [95% CI, 42.0%-57.8%]). With fruquintinib, a complete response was achieved by 1 patient (0.4%; treatment difference, 0.4% [95% CI, −0.3% to 1.1%]), and partial response was achieved by 12 patients (4.3%) in the fruquintinib group vs none

Table 1. Baseline Characteristics (Intention-to-Treat Population) in the Trial of Fruquintinib vs Placebo in Patients With Metastatic Colorectal Cancer

Characteristic	No. (%)[a]	
	Fruquintinib (n = 278)	Placebo (n = 138)
Age, y		
Median (range)	55.0 (23-75)	57.0 (24-74)
<65	228 (82.0)	110 (79.7)
Men	158 (56.8)	97 (70.3)
ECOG performance score of 1[b]	201 (72.3)	101 (73.2)
Body mass index, median (range)	22.9 (16.0-35.4)	23.1 (15.6-30.9)
Time from first diagnosis to randomization, median (range), y	1.8 (0.1-9.7)	2.0 (0.3-9.8)
Colorectal cancer stage at first diagnosis		
I	8 (2.9)	4 (2.9)
II	34 (12.2)	18 (13.0)
III	118 (42.4)	51 (37.0)
IV	117 (42.1)	63 (45.7)
Missing information	1 (0.4)	2 (1.4)
Primary disease site at first diagnosis		
Colon	147 (52.9)	70 (50.7)
Rectum	125 (45.0)	60 (43.5)
Colon and rectum	6 (2.2)	7 (5.1)
Missing information[c]	0	1 (0.7)
Primary tumor location at first diagnosis		
Left (splenic flexure, descending colon, transverse colon, sigmoid colon, and rectum)	214 (77.0)	115 (83.3)
Right (cecum, ascending colon, and hepatic flexure)	56 (20.1)	21 (15.2)
Left and right	4 (1.4)	0
Unknown	4 (1.4)	1 (0.7)
Missing information	0	1 (0.7)
Multiple metastases	265 (95.3)	134 (97.1)
Liver metastasis	185 (66.5)	102 (73.9)
K-*ras* wild-type mutation	157 (56.5)	74 (53.6)
Prior antitumor treatment		
Chemotherapy and pharmacological treatment	278 (100)	138 (100)
Radiation therapy	85 (30.6)	39 (28.3)
Surgery	264 (95.0)	125 (90.6)
Prior systemic chemotherapy (second-line or third-line)	190 (68.3)	98 (71.0)
Prior use of VEGF inhibitors[d]	84 (30.2)	41 (29.7)
Prior use of EGFR inhibitors[e]	40 (14.4)	19 (13.8)
Prior chemotherapy with VEGF and EGFR inhibitors[f]		
Neither	167 (60.1)	83 (60.1)
VEGF only	71 (25.5)	36 (26.1)
EGFR only	27 (9.7)	14 (10.1)
Both	13 (4.7)	5 (3.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] All eligible patients had ECOG PS = 0 or 1 (0 indicates fully active, able to carry on all predisease activities without restriction; 1 indicates restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work).

[c] Referred to cecum.

[d] Included 120 patients who had received bevacizumab (83 in the fruquintinib group and 37 in the placebo group) and 5 patients who had received aflibercept (one in the fruquintinib group and 4 in the placebo group).

[e] Cetuximab.

[f] No patients received VEGFR inhibitor.

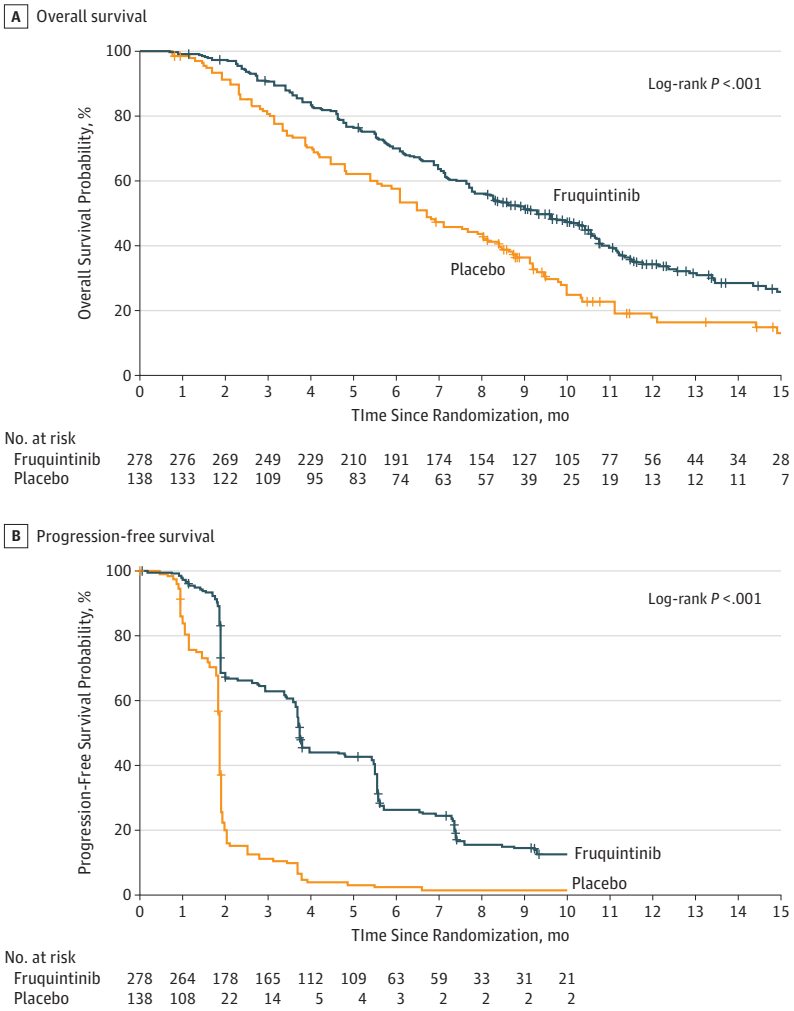
in the placebo group (treatment difference, 4.3% [95% CI, 1.9%-6.7%]). Most of the patients who had a response were still on treatment without disease progression at the cutoff date, hence the median duration of response (5.6 months) was not reached and a 95% CI was not calculable.

Adverse Events

The median treatment exposure was 3.7 months (range, 0.1-21.9 months) for fruquintinib and 1.8 months (range, 0.1-11.1 months) for placebo. The mean relative dose intensity was 92% in the fruquintinib and 98% in the placebo group; the median relative dose intensity was 100% in both groups.

In the safety analysis set, 274 (98.6%) of the 278 patients in the fruquintinib group and 121 (88.3%) of the 137 patients in the placebo group experienced at least 1 treatment-emergent adverse event; among these, 170 (61.2%) patients receiving fruquintinib and 27 (19.7%) receiving placebo experienced a treatment-emergent adverse event of grade 3 or higher severity. Serious adverse events were reported in 43 (15.5%) patients in the fruquintinib group and 8 (5.8%) patients in the

Figure 2. Kaplan-Meier Estimates for Overall Survival and Progression-Free Survival in Patients With Metastatic Colorectal Cancer Receiving Fruquintinib vs Placebo (Intent-to-Treat Population)



All eligible patients had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (0 indicates fully active, able to carry on all predisease activities without restriction; 1 indicates restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature [eg, light housework, office work]). The median follow-up time was 13.3 months (95% CI, 12.1-14.7) for the fruquintinib group and 13.2 months (95% CI, 10.6-19.6) for the placebo group. Tick marks on the curves denote the last known follow-up time for patients with no death date reported.

A, The hazard ratio (HR) for death and corresponding 95% CI for overall population were estimated from a stratified Cox proportional hazards model. Stratified factors included use of vascular endothelial growth factor (VEGF) inhibitor (yes vs no) and K-*ras* gene state (wild type vs mutated). At the planned cutoff date (January 17, 2017), after 297 deaths, the median overall survival was 9.3 (95% CI, 8.2-10.5) months in the fruquintinib group and 6.6 (95% CI, 5.9-8.1) months in the placebo group (HR for death, 0.65 [95% CI, 0.51-0.83]; log-rank *P* < .001).

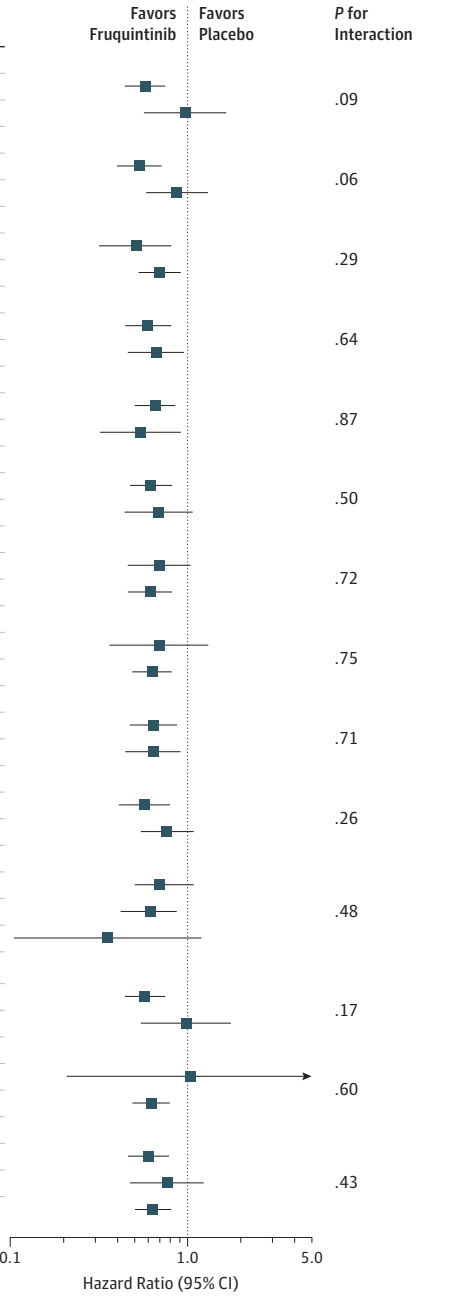
B, The HR for progression-free survival and corresponding 95% CI were estimated from stratified Cox proportional hazards model with treatment as the only covariate. Stratified factors included use of VEGF inhibitors and K-*ras* gene status. Median progression-free survival was also significantly increased with fruquintinib (3.7 months [95% CI, 3.7-4.6] vs 1.8 [95% CI, 1.8-1.8] months with placebo; HR for progression or death, 0.26 [95% CI, 0.21-0.34]; *P* < .001).

placebo group. Forty (14.4%) of the 278 patients treated with fruquintinib and 7 (5.1%) of the 137 patients receiving placebo required hospitalization or prolongation of an existing hospital stay to manage study drug toxicity. The adverse event data are summarized in **Table 2**. The grade 3 to 4 severity adverse events most frequently reported with fruquintinib were hypertension in 59 of 278 patients (21.2%), hand-foot skin reaction in 30 patients (10.8%), and proteinuria in 9 patients (3.2%) (Table 2). Grade 3 hepatic toxicities occurred in 1.5% or less in both treatment groups.

Overall, 11 patients (9 patients receiving fruquintinib [3.2%]; 2 receiving placebo [1.5%]) had fatal treatment-emergent adverse events (Table 2). In the fruquintinib group, these treatment-emergent adverse events were gastrointestinal hemorrhage, death not otherwise specified, lung infection, fungal lower respiratory tract infection, multiple organ dysfunction syndrome, sudden death, bacterial infection, cerebral infarction, and hemoptysis. In the placebo group, these treatment-emergent adverse events were pulmonary embolism and shock (eTable 5 in Supplement 2).

Figure 3. Subgroup Analyses for Overall Survival (Primary Outcome) in Patients With Metastatic Colorectal Cancer Receiving Fruquintinib vs Placebo (Intent-to-Treat Population)

Group	Fruquintinib, No. Deaths	Fruquintinib, No. Total	Placebo, No. Deaths	Placebo, No. Total	Hazard Ratio (95% CI)	*P* for Interaction
Age						
<65	151	228	88	110	0.56 (0.43-0.73)	.09
≥65	37	50	21	28	0.95 (0.55-1.63)	
Sex						
Men	108	158	77	97	0.52 (0.39-0.70)	.06
Women	80	120	32	41	0.85 (0.57-1.29)	
Baseline ECOG PS						
0	50	77	28	37	0.50 (0.31-0.79)	.29
1	138	201	81	101	0.68 (0.52-0.90)	
Time from first metastatic diagnosis to randomization						
≤18 Months	115	163	64	75	0.58 (0.43-0.79)	.64
>18 Months	73	115	45	63	0.65 (0.45-0.94)	
Number of prior treatment lines on metastatic disease						
≤3	146	221	86	107	0.64 (0.49-0.83)	.87
>3	42	57	23	31	0.53 (0.31-0.90)	
Previous chemotherapy lines						
2 or 3	126	190	80	98	0.60 (0.46-0.80)	.50
>3	62	88	29	40	0.67 (0.43-1.05)	
Prior use of VEGF inhibitors						
Yes	60	84	35	41	0.68 (0.45-1.03)	.72
No	128	194	74	67	0.60 (0.45-0.80)	
Prior use of EGFR inhibitors						
Yes	31	40	14	19	0.68 (0.35-1.30)	.75
No	157	238	95	119	0.62 (0.48-0.80)	
Prior targeted treatments						
No anti-VEGF and no anti-EGFR	109	167	63	83	0.63 (0.46-0.86)	.71
Anti-VEGF or anti-EGFR	79	111	46	55	0.63 (0.43-0.90)	
K-RAS status						
Wild type	103	157	56	74	0.56 (0.40-0.78)	.26
Mutated	85	121	53	64	0.75 (0.53-1.07)	
Primary tumor site						
Colon	98	147	55	70	0.68 (0.49-1.07)	.48
Rectum	84	125	46	60	0.60 (0.41-0.86)	
Colon and rectum	6	6	7	7	0.34 (0.10-1.18)	
Primary tumor site at the time of diagnosis[a]						
Left side	141	214	91	115	0.56 (0.43-0.73)	.17
Right side	41	56	16	21	0.96 (0.53-1.75)	
Metastasis						
Single	5	13	2	4	1.03 (0.20-5.37)	.60
Multiple	183	265	107	134	0.61 (0.48-0.78)	
Liver metastasis						
Yes	134	185	85	102	0.59 (0.45-0.77)	.43
No	54	93	24	36	0.75 (0.46-1.21)	
Overall	**188**	**278**	**109**	**138**	**0.62 (0.49-0.79)**	



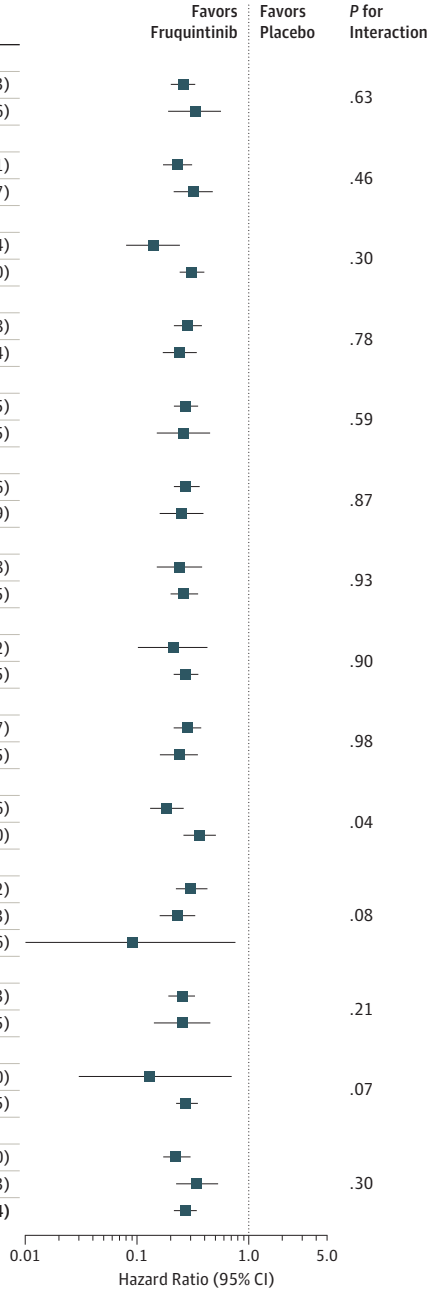
ECOG PS indicates Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

The hazard ratio for death and corresponding 95% CI for each subgroup were estimated from unstratified Cox proportional hazards model with treatment as the only covariate. *P* values were calculated from the Cox model including treatment, subgroup factor, and subgroup factor × treatment interaction term.

Fifty patients (42 receiving fruquintinib [15.1%] and 8 [5.8%] receiving placebo) discontinued treatment due to treatment-emergent adverse events (Table 2). The treatment-emergent adverse event that most frequently led to fruquintinib discontinuation was proteinuria in 6 patients (2.2%). Treatment interruption or dose reduction due to a treatment-emergent adverse event was required by 131 (47.1%) fruquintinib-treated patients and 18 (13.1%) patients receiving placebo. The treatment-emergent adverse events that most commonly led to fruquintinib interruption or dose reduction were hand-foot skin reaction in 37 (13.3%), proteinuria in 27 (9.7%), and decreased platelet counts in 15 (5.4%) patients.

Figure 4. Subgroup Analyses for Progression-Free Survival (Secondary Outcome) in Patients With Metastatic Colorectal Cancer Receiving Fruquintinib vs Placebo (Intent-to-Treat Population)

Group	Fruquintinib, No. Deaths	Fruquintinib, No. Total	Placebo, No. Deaths	Placebo, No. Total	Hazard Ratio (95% CI)	*P* for Interaction
Age						
<65	189	228	101	110	0.26 (0.20-0.33)	.63
≥65	46	50	24	28	0.33 (0.19-0.56)	
Sex						
Men	137	158	88	97	0.23 (0.17-0.31)	.46
Women	98	120	37	41	0.32 (0.21-0.47)	
Baseline ECOG PS						
0	63	77	32	37	0.14 (0.08-0.24)	.30
1	172	201	93	101	0.31 (0.24-0.40)	
Time from first metastatic diagnosis to randomization						
≤18 Months	140	163	68	75	0.28 (0.21-0.38)	.78
>18 Months	95	115	57	63	0.24 (0.17-0.34)	
Number of prior treatment lines on metastatic disease						
≤3	185	221	99	107	0.27 (0.21-0.35)	.59
>3	50	57	26	31	0.26 (0.15-0.45)	
Previous chemotherapy lines						
2 or 3	160	190	91	98	0.27 (0.21-0.36)	.87
>3	75	88	34	40	0.25 (0.16-0.39)	
Prior use of VEGF inhibitors						
Yes	70	84	36	41	0.24 (0.15-0.38)	.93
No	165	194	89	97	0.26 (0.20-0.35)	
Prior use of EGFR inhibitors						
Yes	36	40	16	19	0.21 (0.10-0.42)	.90
No	199	238	109	119	0.27 (0.21-0.35)	
Prior targeted treatments						
No anti-VEGF and no anti-EGFR	140	167	75	83	0.28 (0.21-0.37)	.98
Anti-VEGF or anti-EGFR	95	111	50	55	0.24 (0.16-0.35)	
K-RAS status						
Wild type	133	157	65	74	0.18 (0.13-0.26)	.04
Mutated	102	121	60	64	0.36 (0.26-0.50)	
Primary tumor site						
Colon	125	147	64	70	0.30 (0.22-0.42)	.08
Rectum	105	125	53	60	0.23 (0.16-0.33)	
Colon and rectum	5	6	7	7	0.09 (0.01-0.76)	
Primary tumor site at the time of diagnosis[a]						
Left side	182	214	102	115	0.25 (0.19-0.33)	.21
Right side	45	56	21	21	0.25 (0.14-0.45)	
Metastasis						
Single	10	13	3	4	0.13 (0.03-0.70)	.07
Multiple	225	265	122	134	0.27 (0.22-0.35)	
Liver metastasis						
Yes	160	185	95	102	0.22 (0.17-0.30)	.30
No	75	93	30	36	0.34 (0.22-0.53)	
Overall	**235**	**278**	**125**	**138**	**0.27 (0.21-0.34)**	



ECOG PS indicates Eastern Cooperative Oncology Group Performance Status; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

The hazard ratio for progression or death and corresponding 95% CI for each subgroup were estimated from unstratified Cox proportional hazards model with treatment as the only covariate. *P* values were calculated from the Cox model including treatment, subgroup factor, and subgroup factor × treatment interaction term.

Discussion

This study showed that oral fruquintinib compared with placebo resulted in a statistically significant increase in overall survival among Chinese patients with metastatic CRC who had tumor progression following at least 2 prior chemotherapy regimens.

Fruquintinib is an oral VEGFR inhibitor that has the same mechanism of action as regorafenib, which was approved for third-line treatment of metastatic CRC by the US Food and Drug Administration in September 2014. When this study was conducted, regorafenib was not available in China, and no participants received this drug or any other VEGFR inhibitor prior to or during the study.

Table 2. Summary of Adverse Events Data (Safety Analysis Set) in the Trial of Fruquintinib vs Placebo in Patients With Metastatic Colorectal Cancer

	No. (%)	
	Fruquintinib (n = 278)	Placebo (n = 137)
≥1 Serious adverse event[a]	43 (15.5)	8 (5.8)
≥1 Treatment-related serious adverse event[a,b]	17 (6.1)	2 (1.5)
≥1 Serious adverse event leading to hospitalization or prolongation of hospitalization[a]	40 (14.4)	7 (5.1)
≥1 Treatment-related serious adverse event leading to hospitalization or prolongation of hospitalization[a,b]	17 (6.1)	2 (1.5)
≥1 Treatment-emergent adverse event[c]	274 (98.6)	121 (88.3)
≥1 Treatment-related treatment-emergent adverse event[b,c]	266 (95.7)	97 (70.8)
≥1 Treatment-emergent adverse event ≥ grade 3[c]	170 (61.2)	27 (19.7)
≥1 Treatment-related treatment-emergent adverse event ≥ grade 3[b,c]	128 (46.0)	10 (7.3)
≥1 Treatment-emergent adverse event leading to drug discontinuation[c]	42 (15.1)	8 (5.8)
≥1 Treatment-emergent adverse event leading to drug interruption[c]	98 (35.3)	14 (10.2)
≥1 Treatment-emergent adverse event leading to drug reduction[c]	67 (24.1)	6 (4.4)
≥1 Treatment-emergent adverse event leading to drug interruption or reduction[c]	131 (47.1)	18 (13.1)
≥1 Treatment-emergent adverse event leading to death[a,d]	9 (3.2)	2 (1.5)
Treatment-Related Treatment-Emergent Adverse Events With Overall Rate >10%[b,c,e]		
	All Grades	Grade 3-4	All Grades	Grade 3-4
Hypertension	154 (55.4)	59 (21.2)	21 (15.3)	3 (2.2)
Hand-foot skin reaction[f]	137 (49.3)	30 (10.8)	4 (2.9)	0
Proteinuria	117 (42.1)	9 (3.2)	34 (24.8)	0
Dysphonia	100 (36.0)	0	2 (1.5)	0
TSH level elevated	69 (24.8)	0	3 (2.2)	0
AST level elevated	64 (23.0)	1 (0.4)	14 (10.2)	1 (0.7)
Bilirubin level elevated	56 (20.1)	4 (1.4)	10 (7.3)	2 (1.5)
Diarrhea	56 (20.1)	8 (2.9)	3 (2.2)	0
ALT level elevated	50 (18.0)	2 (0.7)	12 (8.8)	2 (1.5)
Stomatitis	47 (16.9)	1 (0.4)	0	0
Decreased appetite	45 (16.2)	3 (1.1)	11 (8.0)	0
Hypothyroidism	43 (15.5)	0	3 (2.2)	0
Platelet count decreased	37 (13.3)	7 (2.5)	3 (2.2)	0
Occult blood positive	33 (11.9)	0	7 (5.1)	0
Fatigue	33 (11.9)	3 (1.1)	10 (7.3)	0
Weight loss	31 (11.2)	3 (1.1)	5 (3.6)	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; TSH, thyroid-stimulating hormone.

[a] A serious adverse event was defined as any adverse event that resulted in death, was life-threatening, required hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, and included congenital abnormality, birth defect, or other important medical events.

[b] A treatment-related adverse event or serious adverse event was any event that was considered to be related to the study drug treatment according to the physician's subjective judgment.

[c] A treatment-emergent adverse event was defined as an adverse event that started or worsened in severity from at or after the first dose of study medication until 30 d after the date of last study treatment administration. Study drug-related serious adverse events that occurred more than 30 d after the last treatment date were also included as treatment-emergent adverse events.

[d] Specific causes of death are shown in eTable 5 in Supplement 2.

[e] No grade 5 treatment-related treatment-emergent adverse events occurred at an overall rate >10%.

[f] Also known as palmar-plantar erythrodysesthesia syndrome.

In contrast to the treatment patterns in North America and Europe, in China, the VEGF inhibitors bevacizumab and aflibercept are not routinely integrated into first- or second-line therapy. This raises the possibility that results achieved in this study with a VEGFR inhibitor might not generalize to contexts where all patients receive VEGF inhibitors early in their treatment course. The CORRECT trial (regorafenib monotherapy for previously treated metastatic colorectal cancer) compared regorafenib to placebo among 760 patients who had received at least 2 prior chemotherapy regimens including a VEGF inhibitor (typically bevacizumab). In that study, a median survival of 6.4 months was obtained with regorafenib vs 5.0 months with placebo, with an HR for death of 0.77 (95% CI, 0.64-0.94).[12] The CONCUR trial (regorafenib plus best supportive care vs placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer) compared regorafenib and placebo as third-line treatment for 204 Asian patients with metastatic CRC, not all of whom had previously received a VEGF inhibitor, and that study also demonstrated better survival with regorafenib (median 8.8 months, [95% CI, 7.3-9.8]) than placebo (median 6.3 months, [95% CI, 4.8 to 7.6] and an HR for death of 0.55 [95% CI, 0.40-0.77]).[13] In the present study, 30% of patients had received prior VEGF inhibitor therapy, and even in this subgroup, fruquintinib compared with placebo had an HR for death of 0.68 (95% CI, 0.45-1.03) and an HR for progression or death of 0.24 (95% CI, 0.15-0.38).

Systemic chemotherapy can induce VEGF-A and VEGF-C.[11] Currently available VEGF inhibitors (eg, bevacizumab and

aflibercept) shut down tumor angiogenesis by inhibiting the VEGF-A/VEGFR2 pathway while having little effect on VEGFR3 activation and lymphangiogenesis induced by VEGF-C. Fruquintinib has potent activity against all 3 isoforms of VEGFR 1, 2, and 3[20] and at doses of 5 mg once daily, the steady state average trough drug plasma concentration provided a complete and sustained VEGFR inhibition,[15] potentially leading to simultaneous inhibition of tumor angiogenesis and lymphangiogenesis.

The overall incidence of adverse events and serious adverse events was higher in the fruquintinib treatment group than in the placebo group. The most frequently reported adverse events of grade 3 to 4 severity in the fruquintinib treatment group included hypertension, hand-foot skin reaction, proteinuria, and diarrhea. These adverse events have been commonly observed with other VEGF or VEGFR inhibitors.[12,21] Although the incidence of these adverse events in this study was higher with fruquintinib than placebo, most occurred during the first 2 cycles of treatment and could be managed with supportive care and dose adjustment. Furthermore, the duration of fruquintinib treatment was twice as long as that of placebo, hence the adverse event observation periods differed between the 2 treatment groups. This may have contributed to the relatively higher incidence of adverse events and serious adverse events observed with fruquintinib.

Limitations

This study has several limitations. First, the outcomes were evaluated in a purely Chinese population, and further studies will be needed to confirm fruquintinib's efficacy and tolerability in other populations. Second, metastatic CRC standard of care in China differs from that in the Western world in that only one-third of patients had received prior treatment with anti-VEGF or anti-EGFR antibodies. Third, because neither regorafenib nor TAS-102 (tipiracil hydrochloride, a combination of trifluridine and tipiracil hydrochloride)[22] were available in China during the time of study conduct, it was not possible to compare the efficacy of fruquintinib directly with those of regorafenib or TAS-102. Fourth, microsatellite instability status, which can influence prognosis and response to immunotherapy, was not defined.

Conclusions

Among Chinese patients with metastatic CRC who had tumor progression following at least 2 prior chemotherapy regimens, oral fruquintinib compared with placebo resulted in a statistically significant increase in overall survival. Further research is needed to assess efficacy outside China.

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REFERENCES

1. Global Burden of Disease Cancer Collaboration; Fitzmaurice C, Allen C, Barber RM, et al. Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the Global Burden of Disease Study. *JAMA Oncol*. 2017;3(4):524-548. doi:10.1001/jamaoncol.2016.5688

2. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016;66(2):115-132. doi:10.3322/caac.21338

3. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000;355(9209):1041-1047. doi:10.1016/S0140-6736(00)02034-1

4. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947. doi:10.1200/JCO.2000.18.16.2938

5. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004;22(7):1209-1214. doi:10.1200/JCO.2004.11.037

6. Luo HY, Li YH, Wang W, et al. Single-agent capecitabine as maintenance therapy after induction of XELOX (or FOLFOX) in first-line treatment of metastatic colorectal cancer: randomized clinical trial of efficacy and safety. *Ann Oncol*. 2016;27(6):1074-1081. doi:10.1093/annonc/mdw101

7. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol*. 2008;26(12):2013-2019. doi:10.1200/JCO.2007.14.9930

8. Van Cutsem E, Tabernero J, Lakomy R, et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol*. 2012;30(28):3499-3506. doi:10.1200/JCO.2012.42.8201

9. Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1065-1075. doi:10.1016/S1470-2045(14)70330-4

10. Douillard JY, Siena S, Cassidy J, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. *J Clin Oncol*. 2010;28(31):4697-4705. doi:10.1200/JCO.2009.27.4860

11. Tampellini M, Sonetto C, Scagliotti GV. Novel anti-angiogenic therapeutic strategies in colorectal cancer. *Expert Opin Investig Drugs*. 2016;25(5):507-520. doi:10.1517/13543784.2016.1161754

12. Grothey A, Van Cutsem E, Sobrero A, et al; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312. doi:10.1016/S0140-6736(12)61900-X

13. Li J, Qin S, Xu R, et al; CONCUR Investigators. 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(6):619-629. doi:10.1016/S1470-2045(15)70156-7

14. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005;23(5):1011-1027. doi:10.1200/JCO.2005.06.081

15. Cao J, Zhang J, Peng W, et al. A phase I study of safety and pharmacokinetics of fruquintinib, a novel selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3 tyrosine kinases in Chinese patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 2016;78(2):259-269. doi:10.1007/s00280-016-3069-8

16. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. 2013;310(20):2191-2194. doi:10.1001/jama.2013.281053

17. Xu RH, Li J, Bai Y, et al. Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: a phase Ib study and a randomized double-blind phase II study. *J Hematol Oncol*. 2017;10(1):22. doi:10.1186/s13045-016-0384-9

18. Allison PD. *Survival Analysis Using SAS: A Practical Guide*. 2nd ed. Cary, NC: SAS Press; 2010.

19. Jadwiga B. Extensions of Cox model for non-proportional hazards purpose. *Ekonometria*. 2014;3(45):85-101. doi:10.15611/ekt.2014.3.07

20. Sun Q, Zhou J, Zhang Z, et al. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15(12):1635-1645. doi:10.4161/15384047.2014.964087

21. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*. 2004;350(23):2335-2342. doi:10.1056/NEJMoa032691

22. Mayer RJ, Van Cutsem E, Falcone A, et al; RECOURSE Study Group. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919. doi:10.1056/NEJMoa1414325