Subgroup analysis by prior anti-VEGF or anti-EGFR target therapy in FRESCO, a randomized, double-blind, Phase III trial

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Background: FRESCO study demonstrated efficacy and safety of fruquintinib in metastatic colorectal cancer patients. Impact of prior targeted therapy (PTT) on efficacy and safety of fruquintinib was evaluated. **Materials & methods:** In this subgroup analysis of FRESCO trial, patients were divided into PTT and non-PTT subgroups, and efficacy and safety of fruquintinib were assessed, respectively. **Results:**

In non-PTT subgroup, fruquintinib significantly prolonged overall survival (OS) and progression-free survival (PFS) of patients compared with placebo. In PTT subgroup, the median OS and PFS of patients in fruquintinib arm was significantly higher than those in placebo. Treatment-emergent adverse events (TEAEs) rates were similar in both subgroups. **Conclusion:** Fruquintinib demonstrated clinically meaningful improvement in OS, PFS, objective response rate, and disease control rate with manageable TEAEs in both subgroups.

Clinical trial registration: NCT02314819 (ClinicalTrials.gov)

Lay abstract: In this analysis of the FRESCO trial, we evaluated the efficacy and safety of fruquintinib in two different groups of patients (subgroups) with metastatic colorectal cancer - patients who received prior targeted therapy (PTT) and patients who did not (non-PTT). Of the 278 patients treated with fruquintinib, 111 patients received PTT. Patients treated with fruquintinib had longer overall survival and it took longer for their disease to worsen in both PTT and non-PTT subgroups compared with placebo. Patients in both subgroups treated with fruquintinib showed measurable reduction in their tumor size and disease control with similar side effects in patients of both the subgroups. These results suggest that fruquintinib is safe and effective in patients with metastatic colorectal cancer in both subgroups.

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As the most commonly diagnosed cancer and the fourth leading cause of cancer mortality in the world, colorectal cancer (CRC) is also one of the five most common cancers causing 132,100 CRC-related deaths in China [1–3]. The standard of care for metastatic colorectal cancer (mCRC) is chemotherapy as either monotherapy or a combination approach [4–6]. Additionally, targeted agents are also considered standard first- or second-line treatment options in mCRC [7]. These biological agents target either the VEGF/VEGFR pathway or the EGFR pathway. Currently, there are several US FDA-approved targeted therapeutic agents for the treatment of mCRC, namely bevacizumab, cetuximab, ramucirumab, panitumumab, aflibercept, and regorafenib [8–12]. However, in China bevacizumab and cetuximab are the widely used first- and second-line targeted therapeutic agents for the treatment of mCRC [13].

Fruquintinib, a selectively potent VEGFR tyrosine inhibitor, has demonstrated strong antitumor activity in preclinical studies [14,15]. Phase I/II trials demonstrated antitumor activity, clinical benefits in terms of progression-free survival (PFS), and a tolerable safety profile of fruquintinib [16]. A recent Phase III trial (FRESCO) results demonstrated a statistically significant benefit on overall survival (OS) in third-line mCRC patients treated with fruquintinib compared with those treated with placebo [17]. Fruquintinib has been approved by the National Medical Products Administration of China in 2018 for the treatment of mCRC patients who have failed at least two prior systemic antineoplastic therapies including fluoropyrimidine, oxaliplatin, and irinotecan, with or without prior use of anti-VEGF or anti-EGFR therapies.

Several studies have confirmed the clinical benefits of adding of anti-angiogenic agents in mCRC patients who progressed on previous regimens containing VEGF or anti-VEGFR agents [18–21]. However, the exact effect of prior targeted therapy (PTT), especially anti-VEGF therapy, on fruquintinib is still not fully explored. Therefore, we explored the effect of PTT on the efficacy and safety of fruquintinib in patients with mCRC in FRESCO trial.

Materials & methods

Study design, patients & procedures

This study was a subgroup analysis of FRESCO, a multicenter, randomized, double-blind, placebo-controlled, Phase III trial. The study design, procedures, inclusion and exclusion criteria for FRESCO have been previously described in detail [17]. This study included mCRC patients aged 18–75 years with two lines of previous systemic therapy and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The patients were stratified based on prior use of anti-VEGF therapy and *KRAS* mutation status. Previous anti-VEGF or anti-EGFR treatment was allowed, but not mandatory. The patients who previously received other VEGFR inhibitors were excluded.

Eligible patients were randomized into the fruquintinib plus best supportive care (BSC) or placebo plus BSC arms in a 2:1 ratio. The patients in the fruquintinib arm received oral fruquintinib 5 mg once daily for a 28-day treatment cycle (3 weeks on/1 week off), and the patients of the placebo arm received matching placebo. BSC was provided to all the patients throughout the study period.

The study recruitment was during December 2014 to May 2016. This clinical trial is registered with ClinicalTrials.gov (NCT02314819). In the current study, the patients were divided to the PTT and non-PTT subgroups based on whether they had received PTT in the FRESCO intention to treat population. PTT included previously treated anti-VEGF drugs (bevacizumab and aflibercept) or anti-EGFR drugs (cetuximab, nimotuzumab, and panitumumab) or both. The patients who did not receive any PTT were identified as non-PTT subgroup. The patients were also divided into anti-VEGF subgroup and without anti-VEGF subgroup based on previous anti-VEGF treatment history. The median follow-up was 13.3 months for the fruquintinib arm and 13.2 months for the placebo arm.

Outcomes

The efficacy of fruquintinib and placebo was evaluated in terms of OS, PFS, objective response rate (ORR), and disease control rate (DCR). The safety was assessed based on the incidence of any grade and $\geq$ grade 3 drug-related treatment-emergent adverse events (TEAEs). Adverse events were assessed and graded according to the National Cancer Institute, Common Terminology Criteria for Adverse Events version 4.03 during the study period.

Statistical analysis

OS and PFS were analyzed using the Kaplan–Meier method, and an unstratified log-rank test was used to compare treatment effect. The unstratified Cox regression model was used to estimate the hazard ratio (HR) with 95% CIs. The Fisher's exact test was used for comparisons of ORR and DCR. TEAE data were presented as frequencies and proportions. The nominal significance level was set at a two-sided $p = 0.05$ for all statistical tests and no adjustments were made for multiple comparisons. All the statistical analyses were carried out using SAS version 9.2.

Results

Demographic & baseline characteristics

Among 416 randomized patients, 278 were randomized into the fruquintinib arm and 138 were randomized into the placebo arm. A total of 111 patients (39.9%) in the fruquintinib arm (71 with anti-VEGF, 27 with anti-EGFR and 13 with anti-VEGF and anti-EGFR) and 55 patients (39.9%) in the placebo arm were assigned to the PTT group (36 with anti-VEGF, 14 with anti-EGFR and five with anti-VEGF and anti-EGFR). The demographic and baseline characteristics of the 416 patients enrolled in the PTT and non-PTT subgroups of the FRESCO study are shown in [Table 1](#). Baseline characteristics were generally balanced between the placebo and fruquintinib arms ([Table 1](#)).

Efficacy outcomes

Overall survival

Among patients in the non-PTT and PTT subgroups, the survival benefit was significantly higher among patients treated with fruquintinib over placebo ($p < 0.05$). In patients in the PTT and non-PTT subgroups, fruquintinib lowered the risk of death by 37% compared with placebo.

Of non-PTT subgroup patients, the median OS was statistically longer for patients treated with fruquintinib (10.35 months; 95% CI: 8.57–11.07) than those treated with placebo (6.93 months; 95% CI: 5.91–8.77) (HR: 0.63; 95% CI: 0.46–0.86; $p = 0.003$; [Figure 1A](#)). The median OS among the PTT patients was 7.69 months (95% CI: 6.90–10.09) for fruquintinib versus 5.98 months (95% CI: 4.21–8.41) for placebo (HR: 0.63; 95% CI: 0.43–0.90; $p = 0.012$; [Figure 1B](#)). Among patients without previous anti-VEGF treatment (may include patients with prior anti-EGFR treatment), the median OS was statistically longer (10.35 months; 95% CI: 8.44–11.07) in the fruquintinib arm than in the placebo arm (6.93 months; 95% CI: 5.98–8.41) (HR: 0.60; 95% CI: 0.45–0.80; $p < 0.001$; [Figure 1C](#)). For the patients with previous anti-VEGF therapy, the median OS was longer for fruquintinib (7.20 months; 95% CI: 5.85–10.09) than for placebo (5.91 months; 95% CI: 3.88–8.71) (HR: 0.68; 95% CI: 0.45–1.03; $p = 0.066$; [Figure 1D](#)), although the difference did not reach statistical significance, possibly resulted from smaller sample size in this subgroup.

Table 1. Demographic and baseline characteristics.

Variables	Without prior anti-VEGF/anti-EGFR therapy (non-PTT subgroup)		With prior anti-VEGF/anti-EGFR therapy (PTT subgroup)	
	Fruquintinib + BSC (N = 167)	Placebo + BSC (N = 83)	Fruquintinib + BSC (N = 111)	Placebo + BSC (N = 55)
Age, years, n (%)				
– <65	132 (79.0)	67 (80.7)	96 (86.5)	43 (78.2)
– ≥65	35 (21.0)	16 (19.3)	15 (13.5)	12 (21.8)
Gender, n (%)				
– Male	101 (60.5)	57 (68.7)	57 (51.4)	40 (72.7)
– Female	66 (39.5)	26 (31.3)	54 (48.6)	15 (27.3)
ECOG performance status, n (%)				
– 0	46 (27.5)	23 (27.7)	31 (27.9)	14 (25.5)
– 1	121 (72.5)	60 (72.3)	80 (72.1)	41 (74.5)
Primary site at the time of diagnosis				
– Left [†]	128 (76.6)	70 (84.3)	86 (77.5)	45 (81.8)
– Right [‡]	34 (20.4)	11 (13.3)	22 (19.8)	10 (18.2)
– Both left and right	3 (1.8)	0	1 (0.9)	0
– Unknown	2 (1.2)	1 (1.2)	2 (1.8)	0
– Missing	0	1 (1.2)	0	0
Metastatic site				
– Single	9 (5.4)	2 (2.4)	4 (3.6)	2 (3.6)
– Multiple	158 (94.6)	81 (97.6)	107 (96.4)	53 (96.4)
Liver metastasis				
– Yes	108 (64.7)	62 (74.7)	77 (69.4)	40 (72.7)
– No	59 (35.3)	21 (25.3)	34 (30.6)	15 (27.3)
Time from first metastasis diagnosis to randomization (months)				
– Median (min, max)	13.4 (0.9, 66.3)	13.8 (1.9, 68.5)	21.4 (2.2, 79.0)	22.9 (4.2, 81.6)
Length by categorical				
– <18 months	116 (69.5)	55 (66.3)	47 (42.3)	20 (36.4)
– ≥18 months	51 (30.5)	28 (33.7)	64 (57.7)	35 (63.6)
KRAS gene status				
– Wild type	88 (52.7)	43 (51.8)	69 (62.2)	31 (56.4)
– Mutant type	79 (47.3)	40 (48.2)	42 (37.8)	24 (43.6)
Prior treatment lines on or above metastatic disease				
– ≤3	143 (85.6)	74 (89.2)	78 (70.3)	33 (60.0)
– >3	24 (14.4)	9 (10.8)	33 (29.7)	22 (40.0)

[†]Includes splenic flexure, descending colon, transverse colon, sigmoid colon and rectum.
[‡]Includes cecum, ascending colon and hepatic flexure.
 BMI: Body mass index; BSC: Best supportive care; ECOG: Eastern Cooperative Oncology Group; N: Number of planned patients; n: Number of patients; PTT: Prior target therapy; SD: Standard deviation.

Progression-free survival

PFS was significantly longer in the fruquintinib arm in both non-PTT and PTT subgroups ($p < 0.001$) compared with placebo arm (3.81 vs 1.84 months; HR: 0.28; 95% CI: 0.21–0.37; $p < 0.001$); (3.65 vs 1.84 months; HR: 0.24; 95% CI: 0.16–0.35; $p < 0.001$) (Figure 2A & B).

Fruquintinib significantly improved PFS of patients without previous anti-VEGF target therapy (3.81 vs 1.84 months; HR: 0.26; 95% CI: 0.2–0.35; $p < 0.001$) as well as of those with previous anti-VEGF target therapy (3.48 vs 1.84 months; HR: 0.24; 95% CI: 0.15–0.38; $p < 0.001$) (Figure 2C & D).

ORR & DCR

Compared with placebo, patients in the fruquintinib arm demonstrated higher ORR in the PTT (four of 111 patients [3.6] vs 0%; $p = 0.303$) and non-PTT subgroups (nine of 167 patients [5.4] vs 0%; $p = 0.032$). A significantly higher proportion of patients in the fruquintinib arm achieved disease control compared with the

Figure 1. Overall survival for prior targeted therapy and non-prior targeted therapy subgroups. Kaplan-Meier curves showing OS for PTT and non-PTT subgroups. (A) Non-PTT (without anti-VEGF or anti-EGFR treatment); (B) PTT (with prior anti-VEGF or anti-EGFR treatment); (C) without prior anti-VEGF treatment; (D) with prior anti-VEGF treatment. BSC: Best supportive care; HR: Hazard ratio; OS: Overall survival; PTT: Prior targeted therapy.

placebo arm in both PTT (58.6 vs 10.9%; $p < 0.001$) and non-PTT subgroups (64.7 vs 13.3%; $p < 0.001$) (Table 2). The median duration of stable disease in non-PTT and PTT subgroups was 5.6 and 5.5 months, respectively, in the fruquintinib arm and 3.8 and 3.7 months, respectively, in the placebo arm.

Safety

The median duration of treatment of fruquintinib in the non-PTT and PTT subgroups was 5.4 (range: 0.2–21.9) and 2.8 (range: 0.1–18.4) months, respectively. In the placebo arm, the median treatment duration in the non-PTT and PTT subgroups was 1.8 (range: 0.1–11.1) and 1.8 (range: 0.4–4.6) months, respectively.

In the non-PTT subgroup patients, 94.6% of patients treated with fruquintinib experienced drug-related TEAEs, 44.3% experienced grades 3–4, and only one patient (0.6%) had grade 5 TEAEs, which was similar to PTT subgroup patients. 97.3, 45.0, and 2.7% of patients with PTT in the fruquintinib arm experienced drug-related TEAEs of any grade, grades 3–4, and grade 5 TEAEs, respectively (Table 3). Drug-related TEAEs of any grade, grades 3–4, and grade 5 TEAEs, without and with previous anti-VEGF treatment are presented in Table 4.

The most common $\geq$ grade 3 drug-related TEAEs (occurring in $>5\%$ of patients) in the fruquintinib arm of the non-PTT and PTT subgroups were hypertension, hand-foot skin reaction, and proteinuria (only in patients from fruquintinib arm with PTT).

In the non-PTT subgroup, any drug-related TEAEs leading to drug discontinuation was reported in 6.6% of patients in the fruquintinib arm and 1.2% of patients in the placebo arm. Any drug-related TEAEs leading to

Figure 2. Progression-free survival for prior targeted therapy and non-prior targeted therapy subgroups. Kaplan–Meier curves showing PFS for PTT and non-PTT subgroups. **(A)** Non-PTT (without any prior anti-VEGF or anti-EGFR treatment); **(B)** PTT (with prior anti-VEGF or anti-EGFR treatment); **(C)** without prior anti-VEGF treatment; **(D)** with prior anti-VEGF treatment. BSC: Best supportive care; HR: Hazard ratio; PFS: Progression-free survival; PTT: Prior targeted therapy.

drug discontinuation was reported in 9.9% of patients in the fruquintinib arm and none of that in the placebo arm in the PTT subgroup. Any drug-related TEAEs leading to dose reduction were observed in 17.4 and 28.8% of patients in the fruquintinib arm of the non-PTT and PTT group, respectively, and 2.4 and 1.8% of patients in the placebo arm in the non-PTT and PTT group, respectively.

Additionally, the mean relative dose intensity was 90% for fruquintinib versus 100% for placebo, and the median relative dose intensities were 100% for the placebo arms in both the non-PTT and PTT subgroups.

Discussion

This study is a subgroup analysis of the FRESKO trial to show the impact of PTT, including anti-VEGF and anti-EGFR therapies used in the first- and second-line treatment, on the efficacy and safety of fruquintinib in patients with mCRC. Our results confirm the significant clinical benefit of fruquintinib in terms of OS and PFS in the PTT and non-PTT subgroups. The clinical benefits were also observed irrespective of previous anti-VEGF therapy.

Table 2. Prior-therapy analysis of best overall response, objective response rate and disease control rate in study patients.

	Without prior anti-VEGF/anti-EGFR therapy (non-PTT subgroup)		With prior anti-VEGF/anti-EGFR therapy (PTT subgroup)	
	Fruquintinib + BSC (N = 167)	Placebo + BSC (N = 82)	Fruquintinib + BSC (N = 111)	Placebo + BSC (N = 55)
Best overall response, n (%)				
– Complete response, n (%)	0	0	1 (0.9)	0
– Partial response, n (%)	9 (5.4)	0	3 (2.7)	0
– Stable disease, n (%)	99 (59.3)	11 (13.3)	61 (55)	6 (10.9)
– Progression of disease, n (%)	51 (30.5)	57 (68.7)	36 (32.4)	41 (74.5)
– Not assessable, n (%)	8 (4.8)	15 (18.1)	10 (9.0)	8 (14.5)
ORR				
– n (%)	9 (5.4) [†]	0	4 (3.6) [‡]	0
DCR				
– n (%)	108 (64.7) [§]	11 (13.3)	65 (58.6) [§]	6 (10.9)
Duration of stable disease (median [95% CI], months)	5.6 (5.5–7.3)	3.8 (2.8–6.6)	5.5 (3.7–5.5)	3.7 (3.5–4.8)

[†]p = 0.032.
[‡]p = 0.303.
[§]p < 0.001.
 BSC: Best supportive care; DCR: Disease control rate; N: Number of planned patients; n: Number of patients; ORR: Objective response rate; PTT: Prior targeted therapy.

In our study, less than 40% of patients had PTT in the first and or second lines of therapies. In China, a recent study that reviewed medical records from 2011 to 2017, revealed that use of anti-VEGF therapy in first- and second-line treatment of mCRC was 17.8 and 23.3%, respectively [22]. Although, it is pretty low usage of antiangiogenic agents compared with that in north America and Europe. With the facility of reimbursement for bevacizumab since 2017 in China, it has been a trend for opting for bevacizumab added to chemotherapies as first- and/or second-line treatment. Thus, it is necessary to study the impact of prior antiangiogenic therapy on subsequent anti-VEGFR inhibitors in patients with mCRC.

Our study results are in line with published results of randomized trials confirming the clinical benefit of continuing antiangiogenic agents in the treatment of mCRC [8,18,21,23].

Our efficacy results reveal the clinical benefit of fruquintinib in terms of OS and PFS in the PTT and non-PTT subgroups in Chinese mCRC patients. The clinical benefit was also observed irrespective of previous anti-VEGF therapy. A recent meta-analysis comparing regorafenib and fruquintinib concluded that overall, there was a tendency of fruquintinib to be superior to regorafenib, and it was observed that fruquintinib exhibited less toxicity in all-grade toxicity when compared with regorafenib. However, in patients with refractory mCRC similar clinical benefit was observed for both regorafenib and fruquintinib [24].

The safety profile of fruquintinib in our subgroup analysis was similar to that of the main FRESKO study and is on a par with other VEGF/VEGFR inhibitors. In our analysis, the grade ≥ 3 TEAEs were similar in the PTT and non-PTT subgroups of fruquintinib with incidence rates of 45.0 and 44.3%. Among the three most common grade ≥ 3 TEAEs, the incidence of hypertension in the PTT and non-PTT subgroup was similar, with an incidence of 20.7 versus 21.6%, respectively. And, the incidence of hand-foot skin reaction and proteinuria in PTT and non-PTT subgroups were 7.2 versus 13.2% and 5.4 versus 1.8%, respectively. Drug discontinuation (19.8 vs 12.0%) and dose reduction (31.5 vs 19.2%) due to drug-related TEAEs were higher in the PTT subgroup compared with the non-PTT subgroup. While the dose intensity was almost similar in the non-PTT and PTT subgroups, with a mean relative dose intensity of 90% for fruquintinib and 100% for placebo; the median relative dose intensity was 100% for both the fruquintinib and placebo arms in both the subgroups.

There are several limitations of our study: first, the small sample size of the patients who received prior anti-VEGF therapy. Second, our study included only Chinese patients, and hence the findings cannot be generalized as the pattern of antiangiogenic agent's usage in the treatment of mCRC is relatively low in China compared with the western world. Further, research is warranted to evaluate the impact of PTT on efficacy and safety of fruquintinib in mCRC in other populations.

Table 3. Summary of drug-related treatment-emergent adverse events (incidence rate of any grade $\geq 10\%$) by prior targeted therapy/non-prior targeted therapy in the FRESCO study.

Preferred term	Without prior anti-VEGF/anti-EGFR therapy					With prior anti-VEGF/anti-EGFR therapy				
	Fruquintinib + BSC (N = 167), n (%)					Fruquintinib + BSC (N = 111), n (%)				
	All grades	Grades 3–4	Grade 5	All grades	Grades 3–4	Grade 5	All grades	Grades 3–4	Grade 5	Placebo + BSC (N = 55), n (%)
Subjects with any related TEAE	158 (94.6)	74 (44.3)	1 (0.6)	55 (67.1)	4 (4.9)	0	108 (97.3)	50 (45.0)	3 (2.7)	42 (76.4)
Hypertension	93 (55.7)	36 (21.6)	0	12 (14.6)	0	0	61 (55.0)	23 (20.7)	0	9 (16.4)
HFSR	92 (55.1)	22 (13.2)	0	3 (3.7)	0	0	45 (40.5)	8 (7.2)	0	1 (1.8)
Proteinuria	59 (35.3)	3 (1.8)	0	22 (26.8)	0	0	58 (52.3)	6 (5.4)	0	12 (21.8)
Dysphonia	59 (35.3)	0	0	2 (2.4)	0	0	41 (36.9)	0	0	0
AST increased	34 (20.4)	0	0	7 (8.5)	0	0	30 (27.0)	1 (0.9)	0	7 (12.7)
TSH increased	42 (25.1)	0	0	1 (1.2)	0	0	27 (24.3)	0	0	2 (3.6)
Blood bilirubin increased	33 (19.8)	3 (1.8)	0	6 (7.3)	2 (2.4)	0	23 (20.7)	1 (0.9)	0	4 (7.3)
ALT increased	25 (15.0)	1 (0.6)	0	7 (8.5)	0	0	25 (22.5)	1 (0.9)	0	5 (9.1)
Diarrhea	25 (15.0)	3 (1.8)	0	2 (2.4)	0	0	31 (27.9)	5 (4.5)	0	1 (1.8)
Stomatitis	34 (20.4)	0	0	0	0	0	13 (11.7)	1 (0.9)	0	0
Decreased appetite	25 (15.0)	0	0	7 (8.5)	0	0	20 (18.0)	3 (2.7)	0	4 (7.3)
Platelet count decreased	21 (12.6)	2 (1.2)	0	2 (2.4)	0	0	16 (14.4)	5 (4.5)	0	1 (1.8)
Fatigue	19 (11.4)	2 (1.2)	0	7 (8.5)	0	0	14 (12.6)	1 (0.9)	0	3 (5.5)
Weight decreased	18 (10.8)	2 (1.2)	0	2 (2.4)	0	0	13 (11.7)	1 (0.9)	0	3 (5.5)
Occult blood positive	18 (10.8)	0	0	5 (6.1)	0	0	15 (13.5)	0	0	2 (3.6)
Protein urine present	15 (9.0)	2 (1.2)	0	5 (6.1)	0	0	15 (13.5)	1 (0.9)	0	1 (1.8)

BSC: Best supportive care; HFSR: Hand-foot skin reaction; N: Number of planned patients; n: Number of patients; TEAE: Treatment-emergent adverse event; TSH: Thyroid-stimulating hormone.

Table 4. Summary of drug-related treatment-emergent adverse events (incidence rate of any grade $\geq 10\%$) by prior anti-VEGF therapy in the FRESCO study.

Preferred term	Without prior VEGF therapy					With prior VEGF therapy				
	Fruquintinib + BSC (N = 194), n (%)		Placebo + BSC (N = 96), n (%)		Grade 5	Fruquintinib + BSC (N = 84), n (%)		Placebo + BSC (N = 41), n (%)		Grade 5
	All grades	Grades 3–4	Grades 3–4	All grades		All grades	Grades 3–4	All grades	Grades 3–4	
Subjects with any related TEAE	185 (95.4)	83 (42.8)	1 (0.5)	64 (66.7)	0	81 (96.4)	41 (48.8)	33 (80.5)	6 (14.6)	0
Hypertension	106 (54.6)	39 (20.1)	0	15 (15.6)	0	48 (57.1)	20 (23.8)	6 (14.6)	3 (7.3)	0
HFSR	106 (54.6)	24 (12.4)	0	4 (4.2)	0	31 (36.9)	6 (7.1)	0	0	0
Proteinuria	68 (35.1)	3 (1.5)	0	24 (25.0)	0	49 (58.3)	6 (7.1)	10 (24.4)	0	0
Dysphonia	68 (35.1)	0	0	2 (2.1)	0	32 (38.1)	0	0	0	0
AST increased	39 (20.1)	0	0	8 (8.3)	0	25 (29.8)	1 (1.2)	6 (14.6)	1 (2.4)	0
TSH increased	51 (26.3)	0	0	1 (1.0)	0	18 (21.4)	0	2 (4.9)	0	0
Blood bilirubin increased	45 (23.2)	3 (1.5)	0	7 (7.3)	2 (2.1)	11 (13.1)	1 (1.2)	3 (7.3)	0	0
ALT increased	27 (13.9)	1 (0.5)	0	8 (8.3)	0	23 (27.4)	1 (1.2)	4 (9.8)	2 (4.9)	0
Diarrhea	31 (16.0)	4 (2.1)	0	3 (3.1)	0	25 (29.8)	4 (4.8)	0	0	0
Stomatitis	37 (19.1)	0	0	0	0	10 (11.9)	1 (1.2)	0	0	0
Platelet count decreased	26 (13.4)	3 (1.5)	0	2 (2.1)	0	11 (13.1)	4 (4.8)	1 (2.4)	0	0
Occult blood positive	24 (12.4)	0	0	6 (6.3)	0	9 (10.7)	0	1 (2.4)	0	0
Protein urine present	21 (10.8)	2 (1.0)	0	5 (5.2)	0	9 (10.7)	1 (1.2)	1 (2.4)	0	0
Fatigue	23 (11.9)	3 (1.5)	0	7 (7.3)	0	10 (11.9)	0	3 (7.3)	0	0
Decreased appetite	31 (16.0)	1 (0.5)	0	7 (7.3)	0	14 (16.7)	2 (2.4)	4 (9.8)	0	0
Hypothyroidism	33 (17.0)	0	0	3 (3.1)	0	10 (11.9)	0	0	0	0

BSC: Best supportive care; HFSR: Hand-foot skin reaction; N: Number of planned patients; n: Number of patients; TEAE: Treatment-emergent adverse event; TSH: Thyroid-stimulating hormone.

Conclusion

In summary, fruquintinib exhibited significant and clinically meaningful benefit compared with placebo in Chinese mCRC patients in terms of OS and PFS with no unexpected toxicity in both PTT or non-PTT subgroups. The results are consistent with the main FRESCO trial, substantiating the clinical benefit of fruquintinib as third-line treatment for patients with mCRC.

Summary points

- This a subgroup analysis of FRESCO, a randomized, double blind, Phase III study to assess the impact of prior targeted therapy (PTT) on fruquintinib in metastatic colorectal cancer.
- Fruquintinib significantly prolonged overall survival (OS: 10.35 months vs 6.93 months; hazard ratio [HR]: 0.63; $p = 0.003$) and progression free survival (PFS) compared with placebo (median PFS, 3.81m vs 1.84 months; HR: 0.28; $p < 0.001$) in non-PTT group.
- In PTT group also median OS (7.69m vs 5.98 months; HR: 0.63; $p = 0.012$) and PFS (3.65 months vs 1.84 months for placebo; HR: 0.24; $p < 0.001$) was higher in fruquintinib arm compared with placebo arm.
- Patients in the fruquintinib arm of the non-PTT and PTT subgroups demonstrated better objective response rate and disease control rate compared with placebo.
- Treatment-related adverse events were 94.6 and 97.3%, respectively, in non-PTT and PTT subgroups.
- Fruquintinib demonstrated statistically significant and clinically meaningful improvement in survival benefits with manageable toxicity in both subgroups.

Author contributions

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Ethical conduct of research

The study was conducted in accordance to the principles laid down by the Helsinki, 1964, its subsequent amendments, and the Good Clinical Practice Guidelines. Institutional ethical committee approval was obtained from all the study centers. Written informed consent was obtained from all the patients before enrollment into the study.

Data sharing statement

The authors certify that this manuscript reports original clinical trial data: NCT02314819. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data access should comply with local laws and regulations. Data and documents, including the study

protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

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