Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

17 **eTable1. Eligibility Criteria for FRESCO**

Inclusion criteria	Exclusion criteria
• Fully understood the study requirements and voluntarily signed the Informed Consent Form • Histologically or cytologically diagnosed with metastasis CRC (stage IV) • Had failed at least second-line standard chemotherapies including fluorouracil, oxaliplatin, irinotecan regimens (defined as disease progression or intolerable toxicities during the treatment or within 3 months after the last dose) o Each line of treatment for advanced disease until disease progression included one or more chemotherapy drugs used for ≥1 cycle o Previous adjuvant/neoadjuvant therapy was permitted. If relapse or metastasis occurred during the adjuvant/neoadjuvant treatment period or within 6 months after treatment completion, that was considered as failure of first-line systemic chemotherapy o Previous antitumor treatment regimens, including chemotherapy, combined with targeted drugs such as EGFR inhibitors (cetuximab or panitumumab, etc.) or VEGF inhibitors were permitted • Age 18–75 years • Body weight ≥40 kg • ECOG performance status ≤1 (0-1) • Left ventricular ejection fraction ≥50% by echocardiogram test • Evident measurable lesion(s) that met the Response Evaluation Criteria in Solid Tumors version 1.1 • Expected survival >12 weeks.	• Received any systemic antitumor therapies such as chemotherapy or radiotherapy, immunotherapy, biological or hormonal therapy during the 4 weeks preceding the study • Received any prior VEGFR inhibitor treatment (e.g. regorafenib, ramucirumab, apatinib, axitinib, famitinib, or other tyrosine kinase inhibitors) • Absolute neutrophil count $<1.5 \times 10^9$/L, or blood platelet count $<100 \times 10^9$/L, or hemoglobin <90g/L; blood transfusion within 1 week before enrolment for the purpose of enrolment • Serum total bilirubin >1.5 × ULN; ALT and/or AST >2.5 × ULN (subject to the normal value at each site); or ALT and/or AST >5 × ULN for patients with liver metastases • Creatinine clearance rate <50 mL/min • Uncontrolled hypertension, i.e. systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg after monotherapy treatment • Clinically significant electrolyte abnormality • Urine protein detection ≥2+, or urinary protein quantity ≥1.0 g/24 h • Unrecovered toxicity from previous anticancer therapies (NCI CTC AE > grade 1, except for alopecia and ≤ grade 2 neurotoxicity caused by oxaliplatin), or not fully recovered from previous surgeries • Central nervous system metastatic disease or prior cerebral metastasis • Presence of clinically detectable second primary malignant tumors at enrolment, or other malignant tumors within the last 5 years (excluding adequately treated skin basal cell carcinoma or carcinoma in situ of cervix) • Clinically uncontrolled active infection, such as acute pneumonia, active hepatitis B or hepatitis C (previous medical history of

Inclusion criteria	Exclusion criteria
	hepatitis B virus infection regardless of drug control, hepatitis B virus DNA ≥10^4 × copy number or ≥2000 IU/mL) • Difficulty in swallowing or known drug malabsorption • Duodenal ulcer, ulcerative colitis, intestinal obstruction, other gastrointestinal diseases or other conditions that may lead to gastrointestinal bleeding or perforation according to the investigator's judgment; or a history of intestinal perforation or intestinal fistula that were not fully recovered after surgery • History of artery thrombosis or deep venous thrombosis within 6 months before enrollment, or evidence or a history of bleeding tendency within 2 months before the enrollment, regardless of severity • Occurrence of stroke or transient ischemic attack within 12 months before enrolment • Activated partial thromboplastin time and/or prothrombin time >1.5 × ULN (subject to the normal range at each site) • Skin wounds, surgical site, trauma site, severe mucosal ulcers or fracture not completely healed • Acute myocardial infarction, severe/unstable angina or received coronary artery bypass surgery within 6 months prior to enrolment; or patients with cardiac insufficiency of NYHA grade 2 or above • Pregnancy or lactation • Any clinical or laboratory abnormalities or compliance concerns that suggested the patient would be unfit to participate in this clinical trial according to the investigator's judgment • Serious psychological or psychiatric disorders • Participation in any other clinical trial during the 4 weeks preceding the study

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; NCI CTC AE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NYHA, New

York Heart Association; ULN, upper limit of normal; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

24 **eTable 2. Dose Adjustments Induced by Study Treatment-Related Toxicities**

Adverse event (AE)	AE Grading Standard	Dose Adjustment	Treatment Opinions
Hand-foot skin reaction	Grade 1: Numb, paresthesia, dysesthesia, erythema, painless edema, desquamation, thickened skin, or hand and foot discomfort, which does not affect normal activities; all without any pain	Continue treatment with the same dose	Active supportive treatment can be adopted to relieve the symptoms (e.g., urea)
	Grade 2: Erythema with pain accompanied by hand and foot swelling and/or discomfort, which affects normal activities	The treatment can be interrupted; the drug can be reduced to the last dose level should the AE recover to grade 1 within 14 days	Shaoshang Zhitong Ruangao (Wuhan Jianmin Pharmaceutical Group Corp., Ltd.) is recommended
	Grade 3: Wet desquamation, ulcer, blister, severe hand and foot pain or severe discomfort, which affects work or normal activities	The treatment can be interrupted and then resumed or reduced should the AE recover within 7 days; the drug should be reduced to the last dose level if the AE recovers	
Proteinuria	Grade 1: Proteinuria + by urinalysis; 24-hour urine protein quantitation is <1.0 g	Continue treatment with the same dose	
	Grade 2: Proteinuria ++ by urinalysis; 24-hour urine protein quantitation is between 1.0-<2.0g	Continue treatment with the same dose	Active treatment and urinalysis should be performed every week, accompanied by nephrology consultation if necessary
	Grade 2: Proteinuria ++ or higher by urinalysis; 24-hour urine protein quantitation is between 2.0-<3.5g	Treatment can be interrupted, and then reduced to the last dose level should the AE recover to grade 1 within 14 days	Active treatment should be performed, accompanied by nephrology consultation if necessary

Adverse event (AE)	AE Grading Standard	Dose Adjustment	Treatment Opinions
	Grade 3: 24-hour urine protein quantitation ≥3.5g	The drug can be interrupted and then reduced to the last dose should the AE recover to grade 1 within 14 days	Active treatment should be performed, accompanied by nephrology consultation if necessary; and the drug should be terminated should the AE occur for the 3rd time
Hypertension	Grade 1: Prehypertension (SBP 120-139 mmHg or DBP 80-89 mmHg)	None: continue treatment with the same dose	
	Grade 2: SBP 140-159 mmHg or DBP 90-99 mmHg; or DBP symptomatic increase >20 mmHg	Treatment objective: keep BP at or lower than 140/90 mmHg. If the patient has received antihypertensive treatment, the dose of the antihypertensive drug should be increased or other antihypertensive therapies used. If the patient does not receive any antihypertensive treatment, a single antihypertensive therapy should be used	Continue drug treatment with the same dose For the use and dose adjustment of antihypertensive drugs, please refer to the antihypertensive drug treatment guideline and refer to nephrologist for consultation if necessary
	Grade 3: SBP ≥160 mmHg or DBP ≥100 mmHg; or use of more than one antihypertensive drug	Treatment objective: keep BP at or lower than 140/90 mmHg Start antihypertensive drug or increase the dose of the antihypertensive drug in use or adopt additional antihypertensive therapies	For patients with BP exceeding 160/100 mmHg for more than 7 days after using antihypertensive drug or adjusting the dose of the drug used, fruquintinib should be interrupted; should the BP recover to grade 1 or the baseline level, one dose reduction

Adverse event (AE)	AE Grading Standard	Dose Adjustment	Treatment Opinions
		For the use and dose adjustment of antihypertensive drugs, please refer to the antihypertensive drug treatment guideline and ask the nephrologist for assistance if necessary	should be made
	Grade 4: Life-threatening (such as malignant hypertension, temporary or permanent neurological deficits, and hypertensive crisis)	Emergency medical treatment	The drug should be withdrawn
Decreased platelet count	Grade 1: Platelet count of 100~75 × 10^9/L	Continue treatment with the same dose	Perform follow up visit as scheduled
	Grade 2: Platelet count of 75~50 × 10^9/L	The treatment can be interrupted, then continue treatment with the same dose should the AE recover to grade 1 or baseline level within 7 days. The treatment can be interrupted and then reduced to the last dose level should the AE recover to grade 1 or baseline level within 7-14 days	Hematology examination should be performed every 2-3 days; active treatment for platelet elevation is recommended. Hematology examination should be performed once every week during follow up visits
	Grade 3: Platelet count of 50~25 × 10^9/L	The treatment can be interrupted and reduced to the last dose level should the AE recover to grade 1 or baseline level within 14 days	Hematology examination should be performed every 2-3 days; active treatment of platelet elevation or infusion of platelet suspension is recommended. Hematology examination should be performed once every week during follow up

Adverse event (AE)	AE Grading Standard	Dose Adjustment	Treatment Opinions
			visits
	Grade 4: Platelet count <25 × 10^9/L	The study treatment should be withdrawn	Hematology examination should be performed once daily until the AE recovers to grade 2 or lower; infusion of platelet suspension or other active treatment should be provided
Bleeding (any site)	Grade 1	Continue treatment with the same dose	Perform follow up visit as scheduled
	Grade 2	The treatment can be interrupted and then reduced to the last dose level should the AE recover to grade 1 or lower within 14 days	Active treatment
	Grade 3 or above	The study treatment should be withdrawn	Emergency medical intervention
Abnormal liver function (including clinically significant abnormalities such as increasing ALT, AST or total bilirubin)	Grade 1	Continue treatment with the same dose	Perform follow up visit as scheduled
	Grade 2 (with normal baseline value)	Drug interruption can be considered, and the dose should be reduced to the last dose level if the AE recovers to grade 1 or baseline level within 14 days	Active liver protection treatment should be provided, and liver function should be monitored closely once every week
	Grade 2 (with abnormal baseline value)	Continue treatment with the same dose	Active liver protection treatment should be provided, and liver function should be monitored closely once every week
	Grade 3	The drug can be interrupted and then reduced to the last dose level should the AE recover to grade 1	Active liver protection treatment should be provided, and liver function should be monitored closely

Adverse event (AE)	AE Grading Standard	Dose Adjustment	Treatment Opinions
		or baseline level within 14 days	(twice every week until the toxicity recovers to grade 1, baseline level, or can be reasonably explained)
	Grade 4	The study treatment should be withdrawn	Active liver protection treatment should be provided, and liver function should be monitored closely (twice every week until the toxicity recovers to grade 1, baseline level, or can be reasonably explained)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DBP, diastolic blood pressure; SBP, systolic blood pressure.

eTable 3. Summary of Subsequent Anti-Tumor Therapy (Intention-to-Treat Population)

Characteristic	Fruquintinib + best supportive care (n = 278)	Placebo + best supportive care (n = 138)
Patients with subsequent anti-tumor therapy	118 (42.4)	70 (50.7)
Number of subsequent anti-tumor therapies		
0	160 (57.6)	68 (49.3)
1	43 (15.5)	30 (21.7)
≥2	75 (27.0)	40 (29.0)
Type of anti-tumor therapy[a]		
Chemotherapy	90 (32.4)	61 (44.2)
Radiotherapy	19 (6.8)	6 (4.3)
Surgery	13 (4.7)	6 (4.3)
Other	44 (15.8)	23 (16.7)
Post-targeted treatment		
Anti-VEGF/VEGFR, but not EGFR	30 (10.8)	22 (15.9)
Anti-EGFR, but not VEGF/VEGFR	8 (2.9)	6 (4.3)
Both VEGF/VEGFR and EGFR	4 (1.4)	0
Investigational drugs	7 (2.5)	14 (10.1)
Anlotinib/placebo	7 (2.5)	9 (6.5)
APG-1387	0	3 (2.2)
C118P	0	1 (0.7)
Unknown	0	1 (0.7)

Abbreviations: EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

[a]The totals can be >100% since there were patients who received multiple therapies.

eTable 4. Sensitivity Analysis of Overall Survival and Progression-free Survival Data

eTable 4A. Overall Survival – Primary Analysis & Posthoc Sensitivity Analysis 1 – ITT Set

Characteristic	Statistic	Fruquintinib + BSC (N=278)	Placebo + BSC (N=138)
PRIMARY ANALYSIS			
OVERALL SURVIVAL (MONTHS)	Median (95% CI)	9.30 (8.18, 10.45)	6.57 (5.88, 8.11)
	Stratified HR (95% CI)	0.65 (0.51, 0.83)	
POSTHOC SENSITIVITY ANALYSIS			
OVERALL SURVIVAL (MONTHS)	Median (95% CI)	9.30 (8.18, 10.45)	6.57 (5.88, 8.11)
	Stratified HR (95% CI)	0.63 (0.49, 0.81)	

Median overall survival is estimated using Kaplan-Meier method.

HR: Hazard Ratio. HRs and its 95% CIs are calculated from stratified cox proportional hazard models with site as random effect. The stratification factors include prior use of VEGF inhibitor (yes vs. no) and K-Ras gene state (wild type vs. mutant type).

eTable 4B. Overall Survival - Primary Analysis & Posthoc Sensitivity Analysis 2 - Per-Protocol Set

Characteristic	Statistic	Fruquintinib + BSC (N=275)	Placebo + BSC (N=130)
PRIMARY ANALYSIS			
OVERALL SURVIVAL (MONTHS)	Median (95% CI)	9.30 (8.18, 10.45)	6.80 (5.91, 8.38)
	Stratified HR (95% CI)	0.66 (0.52, 0.85)	
POSTHOC SENSITIVITY ANALYSIS			
OVERALL SURVIVAL (MONTHS)	Median (95% CI)	9.30 (8.18, 10.45)	6.80 (5.91, 8.38)
	Stratified HR (95% CI)	0.65 (0.50, 0.83)	

Median overall survival is estimated using Kaplan-Meier method.

HR: Hazard Ratio. HRs and its 95% CIs are calculated from stratified cox proportional hazard models with site as random effect. The stratification factors include prior use of VEGF inhibitor (yes vs. no) and K-Ras gene state (wild type vs. mutant type).

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eTable 4C. Progression-Free Survival – Primary & Posthoc Sensitivity Analyses - ITT Set

Characteristic	Statistic	Fruquintinib + BSC (N=278)	Placebo + BSC (N=138)
PRIMARY ANALYSIS			
PROGRESSION FREE SURVIVAL (MONTHS)	Median (95% CI)	3.71 (3.65, 4.63)	1.84 (1.81, 1.84)
	Stratified HR (95% CI)	0.26 (0.21, 0.34)	
POSTHOC SENSITIVITY ANALYSIS			
PROGRESSION FREE SURVIVAL (MONTHS)	Median (95% CI)	3.71 (3.65, 4.63)	1.84 (1.81, 1.84)
	Stratified HR (95% CI)	0.26 (0.20, 0.33)	

Median progression free survival is estimated using Kaplan-Meier method.

HR: Hazard Ratio. HRs and its 95% CIs are calculated from stratified cox proportional hazard models with site as random effect. The stratification factors include prior use of VEGF inhibitor (yes vs. no) and K-Ras gene state (wild type vs. mutant type).

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eTable 5. Treatment-Emergent Adverse Events Leading to Death (Safety Analysis Set)

System Organ Class Preferred Term	Fruquintinib (n = 278) n (%)	Placebo (n = 137) n (%)
Patients with any treatment-emergent adverse event leading to death	9 (3.2)	2 (1.5)
Death	1 (0.4)	0
Multiple organ dysfunction syndrome	1 (0.4)	0
Sudden death[a]	1 (0.4)	0
Bacterial infection	1 (0.4)	0
Lower respiratory tract infection fungal	1 (0.4)	0
Lung infection	1 (0.4)	0
Gastrointestinal hemorrhage	1 (0.4)	0
Cerebral infarction	1 (0.4)	0
Hemoptysis	1 (0.4)	0
Pulmonary embolism	0	1 (0.7)
Shock	0	1 (0.7)

MedDRA Version 19.1 was used to code adverse events. Patients with more than one treatment-emergent adverse event were counted once at the worst severity category.

[a]Etiologically unknown death.

44 **eTable 6. Exclusion Criteria Leading to Screening Failure**[a]

Criterion Type and Code	Criterion Text	Number of patients who met the exclusion criterion[a]
Exclusion Criterion 1	Absolute neutrophil count (ANC) <1.5x10E9/L, or blood platelet count (PLT) <100x10E9/L, or hemoglobin <9g/dL; blood transfusion within 1 week before enrollment is not allowed;	12
Exclusion Criterion 2	Serum total bilirubin>1.5 x Upper Limit of Normal (ULN), Alanine transaminase (ALT) and/or Aspartate transferase (AST)>1.5xULN; or ALT and/or AST > 3xULN for patients with liver metastases;	10
Exclusion Criterion 3	Creatinine clearance rate < 50mL/min;	5
Exclusion Criterion 4	Uncontrolled hypertension by monotherapy, i.e. systolic blood pressure >140mmHg or diastolic blood pressure >90mmHg after monotherapy treatment.	4
Exclusion Criterion 6	Results of urine protein detection with 2+ or above, or urinary protein quantity >=1.0g/24h;	4
Exclusion Criterion 7	Unrecovered toxicity from previous anticancer therapies, not fully recovered fromprevious surgeries; or the time from the last anticancer therapy or surgery is less than 4 weeks;	2
Exclusion Criterion 8	Central Nervous System (CNS) metastatic disease or prior cerebral metastasis;	2
Exclusion Criterion 10	Clinically uncontrolled active infection, such as acute pneumonia, active hepatitis B or hepatitis C;	2
Exclusion Criterion 12	With gastrointestinal diseases and conditions that may lead to gastrointestinal bleeding or perforation; or with a history of intestinal perforation or intestinal fistula;	9
Exclusion Criterion 13	History of artery thrombosis or deep venous thrombosis within 6 months before enrollment, or have evidence or a history of bleeding tendency within 2 months before the enrollment;	15
Exclusion Criterion 16	Skin wounds, surgical site, trauma site, severe mucosal ulcers or fracture not completely healed;	1
Exclusion Criterion 17	Acute myocardial infarction, severe/unstable angina or received coronary artery bypass surgery within 6 months prior to enrollment; or patients with cardiac insufficiency of NYHA	1

	Grade 2 or above;	
Exclusion Criterion 19	Any clinical or laboratory abnormalities or compliance concerns unfit to participate in this clinical trial according to the investigator's judgment;	10

[a]Six patients met two different exclusion criteria.