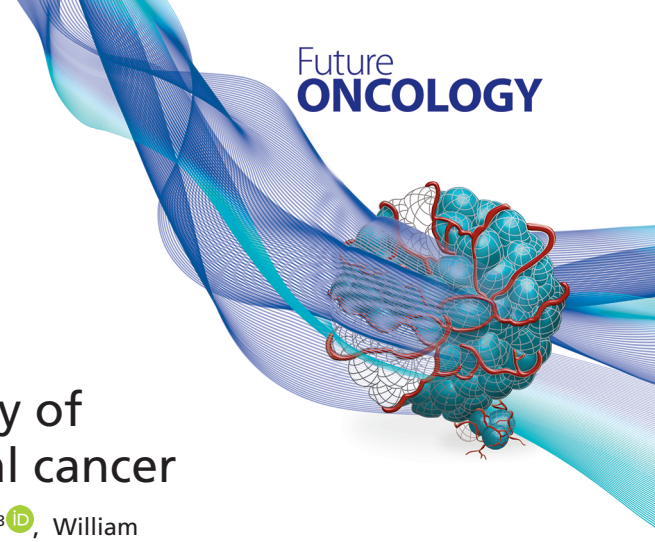
Clinical Trial Protocol



FRESCO-2: a global Phase III study investigating the efficacy and safety of fruquintinib in metastatic colorectal cancer

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Fruquintinib, a novel, highly selective, small-molecule tyrosine kinase inhibitor of VEGF receptors (VEGFRs)-1, -2 and -3, is approved in China for the treatment of metastatic colorectal cancer. FRESCO-2, a global, randomized, double-blind, placebo-controlled, Phase III study, is investigating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. Key inclusion criteria include: progression on or intolerance to TAS-102 and/or regorafenib; and prior treatment with approved chemotherapy, anti-VEGF therapy, and, if *RAS* wild-type, anti-EGFR therapy. Approximately 687 patients will be randomized 2:1 to fruquintinib plus best supportive care or placebo plus best supportive care. Primary and key secondary end points are overall survival and progression-free survival, respectively. FRESCO-2 is enrolling in the USA, Europe, Australia and Japan.

Lay abstract: Fruquintinib is a drug that slows down, reduces or prevents the growth of vessels that supply blood to certain tumors. Fruquintinib is approved in China for the treatment of cancer of the colon and rectum that has spread to these parts of the body from the primary site of cancer: metastatic colorectal cancer. The FRESCO-2 study is being conducted globally to determine how safe and effective fruquintinib is at treating patients with metastatic colorectal cancer that has grown or spread following other forms of treatment, such as chemotherapy. About 687 patients will be enrolled globally to receive either fruquintinib or a matching placebo in a 2:1 ratio, respectively. The FRESCO-2 study is enrolling patients in the USA, Europe, Australia and Japan.

Clinical trial registration: NCT04322539 (ClinicalTrials.gov)

Tweetable abstract: Metastatic colorectal cancer – FRESCO-2 (NCT04322539) is a global, randomized, double-blind, placebo-controlled, Phase III study being conducted to investigate the efficacy and safety of fruquintinib (HMPL-013) plus best supportive care versus matching placebo plus best supportive care in metastatic colorectal cancer.

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Colorectal cancer is a major global health issue. In 2018, an incidence of 1.8 million new cases and 861,000 deaths were estimated worldwide [1]. Metastatic colorectal cancer (mCRC) is incurable by surgical resection in most cases [2,3]. For this reason, treatment principles are primarily aimed at controlling disease progression, prolonging survival, improving tumor-related symptoms and maintaining quality of life (QoL) within the concept of a continuum of care. Survival is longer when patients are exposed to all the available cytotoxics and biological-targeted treatments presumably [3,4]. Approved first- and second-line therapies consist of 5-fluorouracil- [5], irinotecan- [6] and oxaliplatin-based chemotherapy [7]; therapies targeting the VEGF pathway, such as bevacizumab [8–11], aflibercept [12] and ramucirumab [13]; and, if *RAS* wild-type, anti-EGF receptor (anti-EGFR) therapies, such as cetuximab [14–18] and panitumumab [19–21]. For patients whose tumors are V600E *BRAF* mutant, the combination of a *BRAF* inhibitor and cetuximab is approved [22]. In patients with high frequency microsatellite instability (MSI-H)/mismatch repair (MMR)-deficient tumors, nivolumab, nivolumab plus ipilimumab, and pembrolizumab [23–26] are also approved in the USA. Third- or later-line therapies for patients with refractory mCRC include trifluridine/tipiracil hydrochloride (TAS-102) [27] and regorafenib [28]. For patients who have progressed on or are intolerant to these approved therapies, effective treatment options are limited and include reuse of prior therapies (rechallenge chemotherapy) [29–31], enrollment in clinical trials [30] and/or administration of best supportive care (BSC), for example, palliation of tumor-related symptoms [32]. Consequently, there is an unmet medical need for additional safe and effective treatments for patients with refractory mCRC.

Introduction to the study

FRESCO-2, a global, randomized, double-blind, placebo-controlled, multicenter, Phase III study (ClinicalTrials.gov; NCT04322539), is being conducted to investigate the efficacy and safety of fruquintinib (HMPL-013) plus BSC versus matching placebo plus BSC in patients with refractory mCRC who have progressed on or were intolerant to TAS-102 and/or regorafenib. BSC is determined by local clinical practice. Patients also must have been previously treated with standard, approved therapies, including two lines of chemotherapy (fluoropyrimidine, oxaliplatin and irinotecan based), a biological VEGF inhibitor, and, if *RAS* wild-type, an EGFR inhibitor. Patients with MSI-H/MMR-deficient tumors also must have received an immune checkpoint inhibitor, if available and approved. In addition, patients with *BRAF* mutant tumors must also have received a *BRAF* inhibitor, if available and approved. Based on the results from the pivotal Phase III FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) study conducted in China, FRESCO-2 is being conducted to evaluate the efficacy and safety of fruquintinib in a patient population with refractory mCRC that is representative of global treatment practices.

Background & rationale

During tumorigenesis, malignancies release growth factors to induce angiogenesis, which provides nutrients and oxygen for rapid tumor growth. The immature arrangement of endothelial cells on the rapidly growing blood vessels can result in exudation of tumor cells into the circulatory system, through which they may spread to other tissues, leading to metastasis. VEGF is one of the key factors known to induce tumor angiogenesis, and agents that target VEGF and their receptors (VEGFRs) are important therapies for malignant solid tumors, including colorectal cancer [33–35]. These agents directly affect tumor cell function by inhibiting new blood vessel growth and result in vascular regression, normalization and constriction [35,36]. They also offset the effects of chemotherapy induction of VEGF levels [37].

Fruquintinib (HMPL-013) is a potent, highly selective, small-molecule, antitumor, quinazoline-class tyrosine kinase inhibitor (TKI) that was developed by Hutchison MediPharma Limited through *in vitro* and *in vivo* biological screening of a large number of synthetic compounds. *In vitro* studies demonstrated that fruquintinib is highly selective for VEGFRs-1, -2 and -3, which are related to tumor angiogenesis, and has weak or no measurable activity against other kinases [38].

The optimal fruquintinib dose and dosing regimen were determined in a Phase I and Phase Ib/II study [39,40] conducted in China and a Phase I/Ib study [41,42] conducted in the USA. The first of the two studies conducted in China, a Phase I, single-center, open-label, dose-escalation study [39], investigated continuous daily (QD) doses of 1, 2, 4, 5 and 6 mg as well as 5 and 6 mg QD on a regimen of 3 weeks on, 1 week off. Each cycle consisted of 4 weeks. Based on the safety and efficacy results, the maximum-tolerated dose/recommended Phase II dose (RP2D) were determined to be 4 mg QD continuous or 5 mg QD (3 weeks on, 1 week off). The second of the

two studies conducted in China, a Phase Ib/II, randomized, open-label study [40], compared the safety and efficacy of fruquintinib administered orally (PO) 4 mg QD continuous or 5 mg QD, 3 weeks on, 1 week off, to patients with advanced CRC who had failed at least two lines of therapy in order to determine the RP2D. The study also included an expansion stage during which the patients received fruquintinib at the RP2D with the objective of evaluating safety, preliminary efficacy and pharmacokinetic (PK) profile at this dose. The safety profile was better in the 5 mg QD, 3 weeks on, 1 week off, group than the 4 mg QD continuous group. In addition, there was an accumulation of drug over time in the 4 mg QD continuous group. As a result, a 5 mg PO QD, 3 weeks on, 1 week off, dose and regimen were selected as the RP2D and the dosing regimen to be used in subsequent clinical development.

Fruquintinib is approved in China and is indicated for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type, an anti-EGFR therapy. Approval was based on results of the FRESCO Phase III study [43], in which fruquintinib 5 mg PO QD, 3 weeks on, 1 week off, significantly improved median overall survival (OS) in patients with mCRC when compared with placebo (median OS: 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]; $p < 0.001$). Median progression-free survival (PFS) was also significantly improved in the fruquintinib group when compared with the placebo group (3.7 months [95% CI: 3.7–4.6] vs 1.8 months [95% CI: 1.8–1.8]; HR for progression or death: 0.26 [95% CI: 0.21–0.34]; $p < 0.001$). The toxicities of fruquintinib were consistent with those of other VEGF TKIs and were considered manageable [43].

The safety profile of fruquintinib from an ongoing Phase I/Ib study in the USA [41,42] is consistent with that of the clinical studies performed in China, as well as published data for other small-molecule VEGFR inhibitors [39,40]. The PK profile of fruquintinib in the US Phase I/Ib study is also comparable to the PK profile in patients treated with fruquintinib in China at the same dose and dosing regimen of 5 mg PO QD, 3 weeks on, 1 week off, for each 4-week cycle. Preliminary safety and efficacy data from a cohort of patients with refractory mCRC who progressed on all standard therapies, including TAS-102 and/or regorafenib, demonstrated that fruquintinib is generally well-tolerated in heavily pretreated patients with refractory mCRC with less hand–foot syndrome compared with other VEGFR TKIs [42]. There was also evidence of antitumor activity with stabilization of the disease observed in 21 of 31 evaluable patients (disease control rate [DCR]: 80.6%).

The cumulative safety data from the clinical trial program have shown that fruquintinib has an acceptable safety profile that is consistent with other antiangiogenic drugs, particularly small-molecule VEGFR inhibitors. These data provide a strong justification for the investigation of fruquintinib in patients with refractory mCRC globally.

At the time that the FRESCO study was conducted in China (December 2014–January 2017), the standard of care (SOC) for patients with mCRC was different from the current SOC in the USA, Europe, Australia and Japan. Notably, in the FRESCO study, prior therapy included the standard first two lines of cytotoxic chemotherapy (fluoropyrimidine, oxaliplatin and irinotecan based), but only about 30% of patients had received prior therapy with a VEGF inhibitor (bevacizumab), and patients with prior exposure to VEGFR inhibitors, such as regorafenib, were excluded [43]. For this reason, the FRESCO-2 study is being conducted to evaluate fruquintinib in a patient population that is representative of global treatment practices.

Study design & objectives

Eligible patients will be randomized in a 2:1 ratio to receive fruquintinib capsule 5 mg PO QD, 3 weeks on, 1 week off (4-week cycle), plus BSC or matching placebo capsules 5 mg PO QD, 3 weeks on, 1 week off (4-week cycle), plus BSC. The randomization scheme is generated using computer software and loaded into an interactive web response system database. Randomization is stratified by prior therapy (TAS-102 vs regorafenib vs both TAS-102 and regorafenib), *RAS* gene status (wild-type vs mutant) and duration of metastatic disease ($\leq$18 months vs >18 months). Fruquintinib or matching placebo assignment is masked in a double-blind fashion. Crossover between study treatment groups is not permitted. Figure 1 shows the study design schema.

The primary objective of FRESCO-2 is to evaluate the superiority of fruquintinib plus BSC over placebo plus BSC to prolong OS in patients with refractory mCRC. Secondary objectives include the clinical evaluation of fruquintinib in combination with BSC with respect to antitumor activity, safety and tolerability, pharmacokinetic–pharmacodynamic profile, patient reported outcomes (PROs), QoL and healthcare resource utilization. Potential predictive biomarkers of response to fruquintinib are an exploratory objective. Table 1 lists the study objectives and the corresponding study end points.

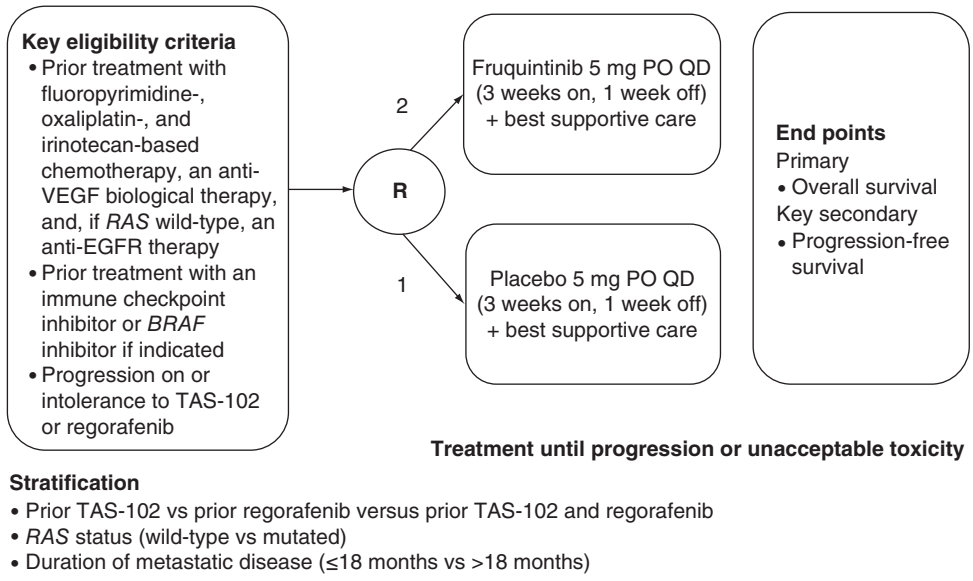

Figure 1. FRESCO-2 Phase III study design schema.
PO: Orally; QD: Daily; R: Randomization; TAS-102: Trifluridine/tipiracil hydrochloride.

Table 1. Study objectives and end points for the FRESCO-2 study.

Objectives	End points
Primary	
Evaluate the potential of fruquintinib to prolong OS	OS
Key secondary	
Evaluate the potential of fruquintinib to prolong PFS	PFS
Secondary	
Evaluate the antitumor activity of fruquintinib in combination with BSC	ORR DCR DoR
Determine the safety and tolerability of fruquintinib in combination with BSC	Occurrence and severity of AEs Relative dose intensity and dose modifications ECGs, vital signs and clinical laboratory abnormalities
Evaluate the PK profile of fruquintinib and the effect of fruquintinib on cardiac repolarization	Plasma concentrations of fruquintinib and metabolite M11 QTc interval
Evaluate the relationship between fruquintinib exposure and end points for efficacy and safety	Exposure-response with efficacy (e.g., OS) and safety (e.g., AEs) end points
Evaluate the effect of fruquintinib on PROs and QoL	Change from baseline in EORTC QLQ-C30 Change from baseline in EQ-5D-5L
Assess impact of fruquintinib on health resource utilization (e.g., hospitalizations, medications)	Reason for resource utilization Type of resource utilization and its duration
Exploratory	
Explore the potential predictive biomarkers of response to fruquintinib	Change from baseline in ctDNA Change from baseline in tumor markers (CEA) Pharmacogenomics

AE: Adverse event; BSC: Best supportive care; CEA: Carcinoembryonic antigen; ctDNA: Circulating tumor deoxyribonucleic acid; DCR: Disease control rate; DoR: Duration of response; ECG: Electrocardiogram; EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L: EuroQol Group, 5-dimension, 5-level health status measure; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PK: Pharmacokinetic; PRO: Patient reported outcome; QoL: Quality of life.

Eligibility criteria

The study population consists of the US, European, Australian and Japanese patients ≥18 years of age (≥20 years in Japan) with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who have received all standard chemotherapies and relevant biologics and progressed on, or were intolerant to, TAS-102 and/or regorafenib. Patients must also have Eastern Cooperative Oncology Group (ECOG) [44] performance status

0 or 1 and have a life expectancy more than 12 weeks. Other key eligibility criteria include: patients with MSI-H or MMR-deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the patient's country unless the patient is ineligible for treatment with a checkpoint inhibitor; patients with *BRAF* mutant tumors must have been treated with a *BRAF* inhibitor if approved and available in the patient's country, unless the patient is ineligible for treatment with a *BRAF* inhibitor; patients must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [45], assessed locally in the patient's country. Box 1 lists the patient eligibility criteria for the FRESCO-2 study.

Box 1. FRESCO-2 patient eligibility criteria

Inclusion criteria

- Age ≥18 years (≥20 years Japan).
- Histologically and/or cytologically documented metastatic colorectal adenocarcinoma. *RAS*, *BRAF* and MSI/MMR status must be documented according to country guidelines.
- Patients must have progressed on or been intolerant to treatment with either TAS-102 or regorafenib. Patients are considered intolerant to TAS-102 or regorafenib if they have received at least one dose of either agent and were discontinued from therapy for reasons other than disease progression. Patients who have been treated with both TAS-102 and regorafenib are permitted. Patients must also have been previously treated with standard approved therapies: fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and, if *RAS* wild-type, an anti-EGF receptor therapy.
- Patients with MSI-H or dMMR tumors must have been treated with immune checkpoint inhibitors if approved and available in the patient's country unless the patient is ineligible for treatment with a checkpoint inhibitor.
- Patients who received oxaliplatin in the adjuvant setting and developed metastatic disease during or within 6 months of completing adjuvant therapy are considered eligible without receiving oxaliplatin in the metastatic setting. Patients who developed metastatic disease more than 6 months after completion of oxaliplatin-containing adjuvant treatment must be treated with oxaliplatin-based therapy in the metastatic setting to be eligible.
- Body weight ≥40 kg.
- ECOG performance status of 0 to 1.
- Have measurable disease according to RECIST v1.1, assessed locally. Tumors that were treated with radiotherapy are not measurable per RECIST v1.1 unless there has been documented progression of those lesions.
- Expected survival >12 weeks.
- For female patients of childbearing potential and male patients with partners of childbearing potential, agreement to use a highly effective form(s) of contraception that results in a low failure rate (<1% per year) when used consistently and correctly, starting during the screening period, continuing throughout the entire study period and for 90 days after taking the last dose of study drug.
- Patients with *BRAF*-mutant tumors must have been treated with a *BRAF* inhibitor if approved and available in the patient's country unless the patient is ineligible for treatment with a *BRAF* inhibitor.

Exclusion criteria

- ANC $<1.5 \times 10^9$/l, platelet count $<100 \times 10^9$/l or hemoglobin <9.0 g/dl. Blood transfusion within 1 week prior to enrollment for the purpose of increasing the likelihood of eligibility is not allowed.
- Serum total bilirubin >1.5 × ULN. Patients with Gilbert syndrome, bilirubin <2 × ULN and normal AST/ALT are eligible.
- ALT or AST >2.5 × ULN in patients without hepatic metastases; ALT or AST >5 × ULN in patients with hepatic metastases.
- Serum creatinine >1.5 × ULN or creatinine clearance <60 ml/min. Creatinine clearance can either be measured in a 24-h urine collection or estimated by the Cockcroft-Gault equation.
- Urine dipstick protein ≥2+ or 24-h urine protein ≥1.0 g/24-h. Patients with greater than 2+ proteinuria by dipstick must undergo a 24-h urine collection to assess urine protein level.
- Uncontrolled hypertension, defined as: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg despite optimal medical management.
- INR >1.5 × ULN or aPTT >1.5 × ULN, unless the patient is currently receiving or intended to receive anticoagulants for prophylactic purposes.
- History of or active gastric/duodenal ulcer or ulcerative colitis, active hemorrhage of an unresected gastrointestinal tumor, history of perforation or fistulas – or any other condition that could, in the investigator's judgment, result in gastrointestinal hemorrhage or perforation – within the 6 months prior to screening.
- History or presence of hemorrhage from any other site (e.g., hemoptysis or hematemesis) within 2 months prior to screening.
- History of a thromboembolic event, including DVT, PE or arterial embolism within 6 months prior to screening.
- Stroke and/or transient ischemic attack within 12 months prior to screening.

- Clinically significant cardiovascular disease, including but not limited to acute myocardial infarction or coronary artery bypass surgery within 6 months prior to enrollment, severe or unstable angina pectoris, New York Heart Association Class III/IV congestive heart failure, ventricular arrhythmias requiring treatment or LVEF <50% by echocardiogram.
- Mean corrected QT interval using the Fridericia method (QTcF) >480 ms or any factors that increase the risk of QTc prolongation or risk of arrhythmic events, such as hypokalemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age in a first-degree relative.
- Concomitant medications with a known risk of causing QT prolongation and/or torsades de pointes.
- Systemic antineoplastic therapies (except for those described below, Brachytherapy[†]) or any investigational therapy within 4 weeks prior to the first dose of study drug, including chemotherapy, radical radiotherapy, hormonotherapy, biotherapy and immunotherapy.
- Systemic, small-molecule targeted therapies (e.g., tyrosine kinase inhibitors) within five half-lives or 4 weeks (whichever is shorter) prior to the first dose of study drug.
- Palliative radiotherapy for bone metastasis/lesion within 2 weeks prior to the initiation of study drug.
- Brachytherapy[†] (i.e., implantation of radioactive seeds) within 60 days prior to the first dose of study drug.
- Use of strong inducers or inhibitors of CYP450 3A4 (CYP3A4) enzyme within 2 weeks (or five half-lives, whichever is longer) before the first dose of study drug.
- Surgery or invasive procedure (i.e., a procedure that includes a biopsy and/or central venous catheter placement is allowed) within 60 days prior to the first dose of study drug or unhealed surgical incision.
- Any unresolved toxicities from a previous antitumor treatment greater than NCI CTCAE v5.0, grade 1 (except for alopecia or neurotoxicity grade ≤2).
- Known HIV infection.
- Known history of active viral hepatitis. For patients with evidence of chronic HBV infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Patients with HCV infection who are currently on treatment are eligible if they have an undetectable HCV viral load. Japanese patients with an unknown history of viral hepatitis must be screened for HBV with hepatitis B surface antigen (HBsAg) and HBV DNA, if indicated, and for HCV with HCV antibody.
- Clinically uncontrolled active infection requiring IV antibiotics.
- Tumor invasion of a large vascular structure (e.g., pulmonary artery, superior or inferior vena cava).
- Women who are pregnant or lactating. Japanese women who temporarily stop lactating will not be permitted and will remain excluded.
- Brain metastases and/or spinal cord compression untreated with surgery and/or radiotherapy and without clinical imaging evidence of stable disease for 14 days or longer; patients requiring steroids within 4 weeks prior to start of study treatment are excluded.
- Other malignancy, except for nonmelanoma skin cancer, *in situ* cervical cancer or bladder cancer (Tis and T1) that have been adequately treated during the 5 years prior to screening.
- Inability to take medication orally, dysphagia or an active gastric ulcer resulting from previous surgery (e.g., gastric bypass) or a severe gastrointestinal disease, or any other condition that investigators believe may affect absorption of the investigational product.
- Other disease, metabolic disorder, physical examination anomaly, abnormal laboratory result or any other condition (e.g., current alcohol or drug abuse) that investigators suspect may prohibit use of the investigational product, affect interpretation of study results, or put the patient at undue risk of harm based on the investigator's assessment.
- Known hypersensitivity to fruquintinib or any of its (or placebo) inactive ingredients including the azo dyes tartrazine – FD&C yellow 5 and sunset yellow FCF – FD&C yellow 6.
- Patients who have received prior fruquintinib.
- Live vaccine ≤28 days before the first dose of study drug(s). Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. Intranasal vaccines are live vaccines and are not allowed.
- Japanese patients who have a history of ILD/noninfectious pneumonitis, have current ILD/pneumonitis or have suspected ILD/pneumonitis that cannot be ruled out by imaging at screening. If ILD is suspected, patients should be evaluated with a chest x-ray, oxygen saturation by pulse oximetry (SpO_2) and so forth to evaluate for evidence of interstitial lung disease.

ANC: Absolute neutrophil count; aPTT: Activated partial thromboplastin time; CTCAE: Common Terminology Criteria for Adverse Events; dMMR: MMR deficient; DVT: Deep vein thrombosis; ECOG: Eastern Cooperative Oncology Group; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ILD: Interstitial lung disease; INR: International normalized ratio; IV: Intravenous; LVEF: Left ventricular ejection fraction; MMR: Mismatch repair; MSI: Microsatellite instability; MSI-H: High frequency microsatellite instability; NCI: National Cancer Institute; PE: Pulmonary embolism; RECIST: Response Evaluation Criteria In Solid Tumors; TAS-102: Trifluridine/tipiracil hydrochloride; ULN: Upper limit of normal.

Planned sample size & study period

The hypothesis is that the addition of fruquintinib to BSC will improve OS compared with the addition of placebo to BSC. Assuming a 10%-yearly dropout rate, a total of 687 patients in a 2:1 randomization ratio and 480 OS events are needed to provide 90% power to detect a HR of 0.73 (fruquintinib vs placebo) for OS at a one-sided significance level of 0.025, which corresponds to an improvement in median OS from 5 months for placebo to 6.8 months for fruquintinib. One prespecified, interim, nonbinding futility analysis is to be performed based on an O'Brien-Fleming stopping boundary for OS when at least 160 events are observed; however, there is no intention to stop the study early for efficacy based on interim OS data. That is, at the time of interim futility analysis, the independent data monitoring committee may recommend stopping the study for futility if the prespecified HR threshold is crossed. Otherwise, the study will continue as planned.

A patient will be considered in the post-TAS-102 or postregorafenib populations if the patient had received at least one dose of TAS-102 or regorafenib prior to entering the study. TAS-102 is more commonly used than regorafenib in clinical practice; hence, the number of randomized postregorafenib patients will be capped at 344 to ensure that no more than 50% of the patients randomized have received regorafenib if there is unanticipated overenrichment of patients with prior regorafenib.

The overall duration planned for the study is approximately 22 months with a 15-month enrollment period starting in July 2020. Approximately 150 sites will be opened for recruitment globally in the USA, Europe, Australia and Japan.

Study procedures

Five milligram QD of fruquintinib or matching placebo is administered PO on days 1–21 of each 28-day cycle. Patients receive fruquintinib or matching placebo until disease progression, unacceptable toxicity or any other protocol-specified criterion for withdrawal occurs, or until the investigator deems that the patient is no longer benefiting from treatment. If required, toxicities are managed by treatment interruptions and dose reductions.

Disease progression and tumor response is assessed using CT or MRI scan in instances where CT is contraindicated, at screening and every 8 weeks until there is progressive disease (PD), death, new antitumor treatment or study completion, whichever comes first. Postdiscontinuation antitumor treatment and survival follow-up after PD will also be recorded. All patients are evaluated utilizing contrast-enhanced CT scan of the chest, abdomen and pelvis, or other acceptable cross-sectional imaging in accordance with RECIST v1.1. The same imaging procedure used to define measurable lesions at baseline is required throughout the study for each patient, unless medically contraindicated.

Safety parameters include adverse events (AEs) and results from laboratory tests, vital signs and echocardiogram (ECG). Safety is assessed throughout and graded based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 [46]. Postdiscontinuation antitumor treatment and survival follow-up after PD also is recorded. Blood samples are collected at various time points to analyze the plasma concentration of fruquintinib and metabolite M11. ECGs and Holter monitoring are collected for routine safety monitoring and for QTc assessment.

PROs and QoL are assessed by change in health status using the cancer-specific European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) [47] and the EuroQol Group, 5-dimension, 5-level health status measure (EQ-5D-5L) [48]. Patients complete PROs and QoL assessments during their screening visit and day 1 of each cycle until treatment is discontinued as well as during their end of treatment follow-up visit.

Potential predictive biomarkers of response to fruquintinib are assessed using pharmacogenomics and by measuring the change from baseline in circulating tumor DNA (ctDNA) and in tumor markers (carcinoembryonic antigen [CEA]). Circulating tumor DNA is assessed at screening and every 8 weeks (±1 week) from cycle 1, day 1 until PD. Serum CEA levels are assessed during screening and day 1 of each cycle until treatment is discontinued as well as during the end of treatment follow-up visit.

To ensure data quality, this study is being conducted in accordance with the ethical principles of the Declaration of Helsinki and in accordance with Good Clinical Practices, including the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. In addition, the protocol is approved by each study site's institutional review board, independent ethics committee or research ethics board, and written informed consent is obtained from each patient at enrollment.

Study end points

The primary end point is OS, and the key secondary end point is PFS. OS is defined as the time (months) from date of randomization to the date of death due to any cause. PFS is defined as the time (months) from date of randomization to the date of the first documented PD by RECIST v1.1 or death due to any cause. The end points for evaluating the antitumor activity of fruquintinib include objective response rate (ORR), DCR and duration of response. ORR is defined as the proportion of patients with a complete response (CR) or partial response (PR), as determined by RECIST v1.1. Duration of response is defined for patients with an objective response as the time (months) from first documentation of a PR or CR to time of first documentation of disease progression or death due to any cause. DCR is defined as the proportion of patients with a CR, PR or stable disease for at least 7 weeks, as determined by RECIST v1.1. Table 1 lists the other secondary and exploratory end points, including ECG corrected QT intervals, plasma concentrations of fruquintinib and metabolite M11, PROs, QoL, healthcare resource utilization (e.g., physician visits, emergency room visits, hospital care [inpatient and outpatient] and drug prescriptions) and candidate predictive biomarker assessments (ctDNA, CEA).

Statistical methods

By treatment group, the intent-to-treat population – all randomly assigned patients – is used for efficacy end points. Safety end points are assessed using the safety population who received at least one dose of study drug according to the treatment received. For OS and PFS, the two-sided p-value from evaluating the treatment effect of fruquintinib is obtained from a stratified log-rank test accounting for randomization stratification factors. Moreover, the HR along with its 95% CI is estimated using a stratified Cox regression model accounting for randomization stratification factors and the event rates over time are estimated using the Kaplan–Meier method. A fixed sequence (hierarchical) testing procedure is used to strongly control the overall Type I error rate at 0.05 in the evaluation of OS and PFS. In addition, sensitivity and subgroup analysis is conducted to evaluate the robustness and consistency of the results from the primary analysis of OS and PFS. ORR and DCR is compared between treatment groups using a stratified Cochran-Mantel-Haenszel test, and the adjusted proportion difference and its 95% CI is calculated.

Conclusion

Given the approval of fruquintinib in China, there is established evidence that fruquintinib plus BSC can provide significant clinical benefit with manageable toxicity in patients with refractory mCRC. FRESCO-2 is an ongoing Phase III study designed to investigate the efficacy and safety of fruquintinib in a patient population that is representative of global treatment practices. The FRESCO-2 study is designed to further demonstrate the superiority of fruquintinib plus BSC over placebo plus BSC in prolonging OS and, therefore, increase the global availability of new treatment options that improve outcomes for patients with refractory mCRC.

Author contributions

A Dasari, AF Sobrero, JC Yao, T Yoshino, WR Schelman, Z Yang, C Chien, M Kania, J Tabernero and C Eng each met the criteria for authorship set forth by the International Committee of Medical Journal Editors: each was involved in the conception, preparation and approval of the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent will be obtained from all participants.

Executive summary

- Globally, there is an unmet medical need for additional safe and effective treatments for patients with refractory metastatic colorectal cancer (mCRC).
- Preclinical and clinical studies conducted in China and the USA have found that fruquintinib (HMPL-013) has antitumor activity in solid tumors, and have shown that fruquintinib has an acceptable level of toxicity that is consistent with other antiangiogenic drugs, particularly small-molecule VEGFR inhibitors.

Background & rationale

- Fruquintinib is a novel, potent and highly selective, small-molecule tyrosine kinase inhibitor of VEGFR-1, -2 and -3.
- VEGFR is one of the key factors known to induce tumor angiogenesis, and agents that target VEGF and the VEGFR are important therapies for malignant solid tumors, including colorectal cancer.
- Five milligram orally daily of fruquintinib is administered on days 1–21 of each 28-day cycle.
- In the FRESCO (Fruquintinib Efficacy and Safety in 3+ Line Colorectal Cancer Patients) Phase III study, which led to the drug's approval in China, fruquintinib improved median overall survival in patients with mCRC in a third-line or later setting when compared with placebo from 6.6 months (95% CI: 5.9–8.1) to 9.3 months (95% CI: 8.2–10.5; hazard ratio for death: 0.65 [95% CI: 0.51–0.83]; $p < 0.001$).
- A clinical trial is needed to evaluate fruquintinib in a patient population representative of current global treatment practices.

Study design & eligibility criteria

- A global, randomized, double-blind, placebo-controlled, multicenter, Phase III study (NCT04322539), FRESCO-2 is being conducted to compare the efficacy and safety of fruquintinib plus best supportive care (BSC) versus placebo plus BSC in refractory mCRC patients.
- The study population will consist of the US, European, Australian and Japanese patients ≥18 years of age (≥20 years in Japan) with histologically and/or cytologically documented metastatic colorectal adenocarcinoma who progressed on, or were intolerant to, all standard chemotherapies, relevant biologics and TAS-102 or regorafenib.
- Approximately 687 patients will be randomized in a 2:1 ratio to receive fruquintinib plus BSC or matching placebo plus BSC.

Outcome measures & end points

- The primary end point is overall survival, and the key secondary end point is progression-free survival.

Conclusion

- The intent of FRESCO-2 is to increase the global availability of new treatment options that improve outcomes for patients with refractory mCRC.

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