FRESCO-2: A Global Phase 3 Study to Investigate the Efficacy and Safety of Fruquintinib in Patients with Metastatic Colorectal Cancer

TPS154

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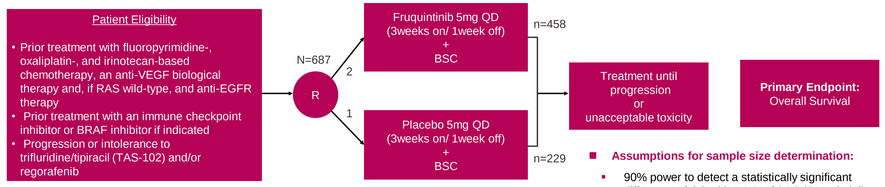
INTRODUCTION

- Patients with metastatic colorectal cancer (mCRC) have limited treatment options following progression on standard therapies. The current standard of care after patients progress on trifluridine/tipiracil (TAS-102) or regorafenib is to re-challenge with previous systemic treatments, enroll in a clinical trial or pursue best supportive care (BSC).
- Fruquintinib (HMPL-013) is a novel, potent and highly selective oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors-1, -2, and -3.[1]
- Fruquintinib was approved in China for patients with refractory metastatic colorectal cancer (mCRC) in September 2018 based on results of the FRESCO trial (NCT02314819),[2] a phase 3 study in patients with refractory mCRC in the 3rd line or later setting. Results showed fruquintinib significantly improved median overall survival (mOS) and median progression-free survival (mPFS) when compared to placebo:
  - mOS: 9.30 vs. 6.57 months (HR=0.65, p<0.001)
  - mPFS: 3.71 vs. 1.84 months (HR=0.26, p<0.001)
  - The toxicities of fruquintinib were manageable.
- A phase 1/1b dose-confirmation study was conducted in the US. Results were previously reported and confirmed the established RP2D in China with similar PK characteristics,[3] and showed preliminary efficacy and safety in patients with refractory mCRC who had progressed on TAS-102 and/or regorafenib.[4]
- At the time FRESCO was conducted in China, the SOC for patients with mCRC differed from that outside of China.
- Here we present an ongoing, global, multicenter, randomized, placebo-controlled phase 3 trial (FRESCO-2; 2019-013-GLOB1; NCT04322539) being conducted to investigate the efficacy and safety of fruquintinib plus BSC to placebo plus BSC in patients with refractory mCRC.

METHODS

- FRESCO-2 is open and enrolling in the US, Europe and Japan and is anticipated to open in Australia in Q1 2021.
- A safety lead-in phase is being conducted in 6 patients in Japan prior to opening enrollment to the randomized portion of the study.
- Eligible patients must have mCRC and have progressed on or been intolerant to all standard chemotherapies, relevant biologics and TAS-102 or regorafenib or both.
- Best supportive care is determined by local clinical practice.

FRESCO-2 STUDY DESIGN



Stratification factors:
Prior TAS 102 vs. prior regorafenib vs prior TAS 102 and regorafenib
RAS status (WT vs MT)
Duration of metastatic disease (≤18 months vs > 18 months

Assumptions for sample size determination:

- 90% power to detect a statistically significant difference of OS with a **HR of 0.73** (Fruquintinib vs placebo), an improvement in mOS from 5 months for placebo to 6.8 months for fruquintinib
- Overall duration of study is 22 months with 15 months accrual period
- 10% yearly dropout rate
- Final analysis at 480 OS events with an interim futility analysis at 160 OS events

KEY INCLUSION CRITERIA

- Histologically or cytologically documented metastatic colorectal adenocarcinoma. RAS, BRAF, and microsatellite instability (MSI)/mismatch repair (MMR) status must be documented.
- Patients must have progressed on or been intolerant to treatment with trifluridine/tipiracil (TAS-102) and/or regorafenib. Patients are considered intolerant to TAS-102 or regorafenib if they have received at least 1 dose of either agent and were discontinued from therapy for reasons other than disease progression. 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-EGFR therapy).
- Patients with microsatellite-high (MSI-H) or mismatch repair deficient (dMMR) tumors must have been treated with immune checkpoint inhibitors if approved and available in the subject's country unless subject 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 subject's country unless subject is ineligible for treatment with a BRAF inhibitor.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1.
- Have measurable disease according to RECIST version 1.1, assessed locally.
- Expected survival >12 weeks.

KEY EXCLUSION CRITERIA

- Absolute neutrophil count (ANC) <1.5×10^9/L, platelet count <100×10^9/L, or hemoglobin <9.0 g/dL.
- Serum total bilirubin >1.5 × the upper limit of normal (ULN). Patients with Gilbert syndrome, bilirubin <2 × ULN, and normal AST/ALT are eligible.
- Alanine aminotransferase (ALT) or aspartate aminotransferase (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.
- Urine dipstick protein ≥2+ or 24-hour urine protein ≥1.0 g/24-h.
- Uncontrolled hypertension: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg.
- International normalized ratio (INR) >1.5 × ULN or activated partial thromboplastin time (aPTT) >1.5 × ULN, unless the patient is currently receiving anticoagulants.
- History or presence of hemorrhage from within 2 months prior to screening.
- History of a thromboembolic event within 6 months prior to screening.
- Stroke and/or transient ischemic attack within 12 months prior to screening.
- Clinically significant cardiovascular disease within 6 months prior to enrollment.

OBJECTIVES

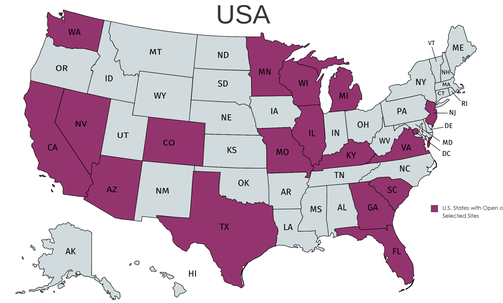
Primary Objective	Primary Endpoint
Evaluate the potential of fruquintinib to prolong OS	• OS
Key Secondary Objective	**Key Secondary Endpoint**
Evaluate the potential of fruquintinib to prolong PFS	• PFS
Secondary Objectives	**Secondary Endpoints**
Evaluate the anti-tumor activity of fruquintinib in combination of BSC	• Objective response rate • Disease control rate • Duration of objective response
Determine the safety and tolerability of fruquintinib in combination of BSC	• Occurrence and severity of AEs • Relative dose intensity and dose modifications • ECG and clinical laboratory abnormalities
Evaluate the pharmacokinetic (PK) profile and the effect of fruquintinib on cardiac repolarization	• Plasma concentrations of fruquintinib and M11 • QTc interval
Evaluate the relationship between fruquintinib exposure and endpoints for efficacy and safety	• Exposure-response with efficacy (eg, OS) and safety (eg, AEs) endpoints
Evaluate the effects fruquintinib on PROs	• Changes from baseline in EORTC QLQ-C30 • Changes from baseline in EQ-5D-5L
Assess the impact of fruquintinib on health resource utilization	• Reason of resource utilization • Type of resource utilization and its duration
Exploratory Objectives	**Exploratory Endpoints**
Explore the potential predictive biomarkers of response to fruquintinib	• Change from baseline ctDNA • Change from baseline CEA

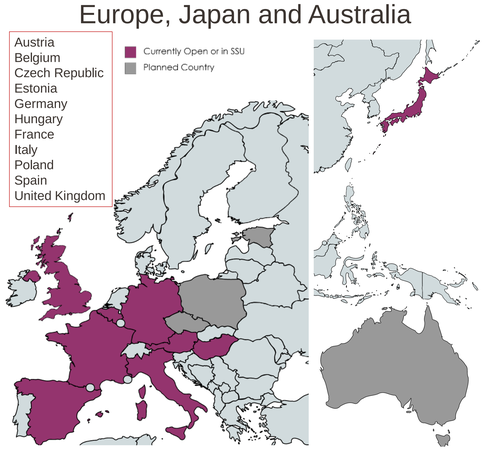
STATISTICAL ANALYSIS

Key aspects of the planned analyses for OS and PFS

- Kaplan-Meier method will be used to summarize the data;
- Two-sided p-value will be calculated using a stratified log-rank test accounting for randomization stratification factors;
- HR and its 95% confidence interval will be obtained from a Cox proportional hazard model;
- A fixed-sequence (hierarchical) testing procedure will be used to control the overall type I error rate at 0.05;
- Sensitivity and subgroup analysis will be conducted to evaluate the robustness and consistency of the results from the primary analysis.

PARTICIPATING CENTERS





DISCLOSURES

W Schelman, S Nanda, C Chien, and M Kania are employed by Hutchison MediPharma

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References

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