Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study

Arvind Dasari, Sara Lonardi*, Rocio Garcia-Carbonero, Elena Elez, Takayuki Yoshino, Alberto Sobrero, James Yao, Pilar García-Alfonso, Judit Kocsis, Antonio Cubillo Gracian, Andrea Sartore-Bianchi, Taroh Satoh, Violaine Randrian, Jiri Tomasek, Geoff Chong, Andrew Scott Paulson, Toshiki Masuishi, Jeremy Jones, Tibor Csőszi, Chiara Cremolini, Francois Ghiringhelli, Ardaman Shergill, Howard S Hochster, John Krauss, Ali Bassam, Michel Ducreux, Anneli Elme, Laurence Faugeras, Stefan Kasper, Eric Van Cutsem, Dirk Arnold, Shivani Nanda, Zhao Yang, William R Schelman, Marek Kania, Josep Tabernero†, Cathy Eng†, on behalf of the FRESCO-2 Study Investigators‡*

Summary

Background There is a paucity of effective systemic therapy options for patients with advanced, chemotherapy-refractory colorectal cancer. We aimed to evaluate the efficacy and safety of fruquintinib, a highly selective and potent oral inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1, 2, and 3, in patients with heavily pretreated metastatic colorectal cancer.

Methods We conducted an international, randomised, double-blind, placebo-controlled, phase 3 study (FRESCO-2) at 124 hospitals and cancer centres across 14 countries. We included patients aged 18 years or older (≥20 years in Japan) with histologically or cytologically documented metastatic colorectal adenocarcinoma who had received all current standard approved cytotoxic and targeted therapies and progressed on or were intolerant to trifluridine–tipiracil or regorafenib, or both. Eligible patients were randomly assigned (2:1) to receive fruquintinib (5 mg capsule) or matched placebo orally once daily on days 1–21 in 28-day cycles, plus best supportive care. Stratification factors were previous trifluridine–tipiracil or regorafenib, or both, *RAS* mutation status, and duration of metastatic disease. Patients, investigators, study site personnel, and sponsors, except for selected sponsor pharmacovigilance personnel, were masked to study group assignments. The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. A non-binding futility analysis was done when approximately one-third of the expected overall survival events had occurred. Final analysis occurred after 480 overall survival events. This study is registered with ClinicalTrials.gov, NCT04322539, and EudraCT, 2020-000158-88, and is ongoing but not recruiting.

Findings Between Aug 12, 2020, and Dec 2, 2021, 934 patients were assessed for eligibility and 691 were enrolled and randomly assigned to receive fruquintinib (n=461) or placebo (n=230). Patients had received a median of 4 lines (IQR 3–6) of previous systemic therapy for metastatic disease, and 502 (73%) of 691 patients had received more than 3 lines. Median overall survival was 7·4 months (95% CI 6·7–8·2) in the fruquintinib group versus 4·8 months (4·0–5·8) in the placebo group (hazard ratio 0·66, 95% CI 0·55–0·80; p<0·0001). Grade 3 or worse adverse events occurred in 286 (63%) of 456 patients who received fruquintinib and 116 (50%) of 230 who received placebo; the most common grade 3 or worse adverse events in the fruquintinib group included hypertension (n=62 [14%]), asthenia (n=35 [8%]), and hand-foot syndrome (n=29 [6%]). There was one treatment-related death in each group (intestinal perforation in the fruquintinib group and cardiac arrest in the placebo group).

Interpretation Fruquintinib treatment resulted in a significant and clinically meaningful benefit in overall survival compared with placebo in patients with refractory metastatic colorectal cancer. These data support the use of fruquintinib as a global treatment option for patients with refractory metastatic colorectal cancer. Ongoing analysis of the quality of life data will further establish the clinical benefit of fruquintinib in this patient population.

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*Joint first authors

†Joint senior authors

‡Members listed in the appendix (pp 2–5)

Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX, USA (A Dasari MD, Prof J Yao MD); **Medical Oncology Unit 1, Veneto Institute of Oncology IOV-IRCCS Padua, Padua, Italy** (S Lonardi MD); **Oncology Department, Hospital Universitario 12 de Octubre, Imas12, UCM, Madrid, Spain** (R Garcia-Carbonero MD); **Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology, Universitat Autònoma de Barcelona, Barcelona, Spain** (E Elez MD); **Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan** (Prof T Yoshino MD); **Department of Medical Oncology, Azienda Ospedaliera San Martino, Genoa, Italy** (Prof A Sobrero MD); **Medical Oncology Service, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón (IiSGM), Universidad Complutense, Madrid, Spain** (Prof P García-Alfonso MD); **Department of Oncoradiology, Bács -Kiskun Megyei Oktatókórház, Kecskemét, Hungary** (J Kocsis MD); **Medical Oncology, Hospital Universitario HM Sanchinarro**

Introduction

Colorectal cancer is the third most diagnosed cancer and second leading cause of cancer-related deaths worldwide.[1] Approximately 50% of patients with colorectal cancer develop distant metastases during their disease course; the overall 5-year survival rate for such patients is 15%.[2,3] Standard initial systemic treatments for metastatic colorectal cancer include chemotherapy and targeted therapies, as appropriate.[3,4] Later-line non-selective treatment options include the oral agents trifluridine–tipiracil and regorafenib, a multikinase inhibitor, which have shown incremental effects on median overall survival.[5,6] Consequently, there is an unmet need for safe and effective treatments for

Centro Integral Oncológico Clara Campal, Madrid, Spain (A Cubillo Gracian MD); **Grande Ospedale Metropolitano Niguarda, Milan, Italy** (A Sartore-Bianchi MD); **Department of Oncology and Hemato-Oncology, Università degli Studi di Milano, Milan, Italy** (A Sartore-Bianchi); **Palliative and Supportive Care Center, Osaka University Hospital, Osaka, Japan** (T Satoh MD); **Department of Hepato-Gastroenterology, CHU Poitiers, Université de Poitiers, Poitiers, France** (V Randrian MD); **Department of Complex Oncology Care, Masaryk Memorial Cancer Institute, Brno, Czech Republic** (J Tomasek MD); **Olivia Newton-John Cancer Wellness & Research Centre, Austin Hospital, Melbourne, VIC, Australia** (G Chong MD); **Texas Oncology–Baylor Charles A Sammons Cancer Center, US Oncology Research, Dallas, TX, USA** (A S Paulson MD); **Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan** (T Masuishi MD); **Division of Hematology and Medical Oncology, Mayo Clinic Cancer Center, Jacksonville, FL, USA** (J Jones MD); **Hetényi Géza Kórház, Onkológiai Központ, Szolnok, Hungary** (T Csőszi MD); **Department of Translational Research and New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy** (Prof C Cremolini MD); **Department of Medical Oncology, Centre Georges François Leclerc, Dijon, France** (Prof F Ghiringhelli MD); **University of Chicago, Biological Sciences Division, Chicago, IL, USA** (A Shergill MD); **Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA** (Prof H S Hochster MD); **Department of Medicine, University of Michigan, Ann Arbor, MI, USA** (J Krauss MD); **Békés Megyei Központi Kórház, Pándy Kálmán Tagkórház, Megyei Onkológiai Központ, Gyula, Hungary** (A Bassam MD); **Gustave Roussy Cancer Center, Inserm U1279 Tumors Cell Dynamics, Université Paris Saclay, Villejuif, France** (Prof M Ducreux MD); **Oncology and Haematology Clinic, North Estonia Medical Centre, Tallinn, Estonia** (A Elme MD);

Research in context

Evidence before this study

We searched PubMed on Dec 2, 2022, for clinical trials published in English from Jan 1, 2015, to Dec 31, 2019, using the terms ("refractory colorectal cancer" OR "metastatic colorectal cancer") AND ("phase III" OR "phase 3") AND ("tyrosine kinase inhibitor" OR "vascular endothelial growth factor" OR "vascular endothelial growth factor receptor" OR "VEGFR" OR "multikinase inhibitor" OR "regorafenib" OR "TAS-102" OR "trifluridine/tipiracil"). The search yielded 35 results. Studies were reviewed if they were conducted in patients receiving third-line or later therapy for metastatic colorectal cancer and reported primary endpoint results. We identified six relevant randomised phase 3 studies evaluating trifluridine–tipiracil (two studies), regorafenib (two studies), nintedanib (one study), and our previous study of fruquintinib in China (FRESCO). Trifluridine–tipiracil, an oral chemotherapy, and regorafenib, a multikinase inhibitor, have both shown incremental benefit in overall survival and progression-free survival in patients with metastatic colorectal cancer who have progressed on standard therapies, but can be associated with treatment-related toxicities that require dose reductions. Fruquintinib is a highly selective and potent oral inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFRs) 1, 2, and 3. In the FRESCO study, fruquintinib showed significant improvement in both overall survival and progression-free survival compared with placebo. However, at the time of the study, standard treatment practices for metastatic colorectal cancer in China were not the same as the standard treatment practices outside of China; only one-third of the patients had received previous anti-VEGF therapy, and none had received trifluridine–tipiracil or regorafenib. The multikinase inhibitor nintedanib failed to improve overall survival in this setting. Thus, we concluded that there was an unmet clinical need for an international, randomised, phase 3 study to assess the efficacy and safety of fruquintinib in patients with previous treatment representative of current global treatment practices, which includes treatment with trifluridine–tipiracil or regorafenib, or both.

Added value of this study

Patients with surgically unresectable metastatic colorectal cancer have few treatment options. Trifluridine–tipiracil and regorafenib are both widely approved in previously treated patients and have shown marginal benefit in median overall survival. To our knowledge, FRESCO-2 is the first study to show efficacy of an oral VEGFR inhibitor in patients who have received previous trifluridine–tipiracil or regorafenib, or both. The observed reduction in the overall risk of death and risk of progression or death with fruquintinib compared with placebo suggests that inhibition of the VEGF pathway remains an effective management strategy for metastatic colorectal cancer, even in the later-line setting and in patients with previous exposure to anti-angiogenic agents. The findings from FRESCO-2 show that fruquintinib is effective and well tolerated in a broad population of patients with heavily pretreated metastatic colorectal cancer.

Implications of all the available evidence

This study shows that targeted inhibition of VEGFRs with fruquintinib is a safe and effective treatment approach for patients with metastatic colorectal cancer who had disease progression on or were intolerant to trifluridine–tipiracil or regorafenib, or both. The results presented here support findings from previous studies showing the efficacy and tolerability of fruquintinib monotherapy in patients with fewer previous lines of therapy (eg, FRESCO). Thus, the totality of evidence for fruquintinib supports its use in multiple settings and it should be considered as a new global treatment option for patients with chemotherapy-refractory metastatic colorectal cancer, for whom there are a paucity of treatment options. Additional research will be needed to determine the optimal sequencing strategy for patients who have failed at least two lines of therapy.

patients with refractory metastatic colorectal cancer. Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor of vascular endothelial growth factor (VEGF) receptors (VEGFRs) 1, 2, and 3,[7] which are key regulators of angiogenesis associated with tumour growth and metastasis.[7–9] In the phase 3 FRESCO study (NCT02314819),[10] in patients with metastatic colorectal cancer who had received at least two previous lines of chemotherapy, treatment with fruquintinib resulted in significant improvement compared with placebo in overall survival (median 9·3 months [95% CI 8·2–10·5] *vs* 6·6 months [5·9–8·1]; hazard ratio [HR] 0·65 [95% CI 0·51–0·83]; p<0·001) and progression-free survival (median 3·7 months [3·7–4·6] *vs* 1·8 months [1·8–1·8]; HR 0·26 [0·21–0·34]; p<0·001). These results led to the approval of fruquintinib in China in 2018. However, at the time of the FRESCO study,[10] standard treatment practices and available therapies for metastatic colorectal cancer in China differed from the rest of the world; in China, VEGF inhibitors or epidermal growth factor receptor (EGFR) inhibitors were not routinely included into the standard of care, and regorafenib and trifluridine-tipiracil were not yet approved. Thus, in FRESCO, only 30% of patients had received previous treatment with a VEGF inhibitor and 14% had previously received an EGFR antibody, none had received trifluridine–tipiracil, and patients who had received regorafenib were excluded.[10] An ongoing phase 1/1b expansion cohort study (NCT03251378) of fruquintinib in the USA, which included patients with metastatic colorectal cancer with or without previous trifluridine–tipiracil or regorafenib, showed encouraging preliminary anti-tumour efficacy and safety,[11] further supporting the investigation of fruquintinib in a population with refractory metastatic colorectal cancer.

We aimed to evaluate the efficacy and safety of fruquintinib in patients with heavily pretreated metastatic colorectal cancer.

Methods

Study design and participants

We conducted an international, randomised, double-blind, placebo-controlled, phase 3 study (FRESCO-2) at 124 hospitals and cancer centres across 14 countries in North America, Europe, Asia, and Australia.[12] Eligible patients were aged 18 years or older (≥20 years in Japan) with histologically or cytologically documented metastatic colorectal adenocarcinoma, who had received all standard treatments, including fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, anti-VEGF therapy, and anti-EGFR therapy (if *RAS* wild type), and had disease progression on or been intolerant to trifluridine–tipiracil or regorafenib. *RAS*, *BRAF*, and microsatellite instability or mismatch repair status had to be documented. Patients with deficient mismatch repair or microsatellite instability-high tumours must have also received an immune-checkpoint inhibitor and those with *BRAFV600E*-mutant tumours must have also received a BRAF inhibitor, if approved and available in that country. Other eligibility criteria included an Eastern Cooperative Oncology Group performance status score of 0–1 and measurable disease by Response Evaluation Criteria in Solid Tumours (RECIST; version 1.1), assessed locally. Complete eligibility criteria are provided in the appendix (pp 6–8).[12]

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines, including the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The protocol and amendments (available in the appendix [pp 133–269]) were approved by the institutional review board and independent ethics committee at each participating site. All participants provided written informed consent at enrolment.

Randomisation and masking

Eligible patients were assigned an identification number by an interactive web response system and were randomly assigned (2:1) to receive fruquintinib or placebo, plus best supportive care. Randomisation was done centrally by a secure interactive web response system (Endpoint IRT PULSE) using randomised block size of 3. Stratification factors were previous therapy (trifluridine–tipiracil or regorafenib, or both), *RAS* mutation status (wild type *vs* mutant), and duration of metastatic disease (≤18 months *vs* >18 months). To prevent unintentional enrichment, the number of patients treated with previous regorafenib was limited to 50% of the total randomly assigned patients. Only authorised, unmasked personnel from Endpoint and the contract research organisation had access to the interactive web response system based on established criteria. When randomisation was performed by a site in the system, the site accessed the secure system to enter patient data and the randomisation number was assigned automatically by the Endpoint IRT system. No user had the ability to assign patients manually. All patients, investigators, study site personnel, and sponsors in regular contact with the study site, except for selected sponsor pharmacovigilance personnel, were masked to group assignments throughout the study.

Procedures

Patients received fruquintinib (5 mg capsule) or matched placebo orally once daily on days 1–21 in 28-day cycles. Treatment continued until disease progression, death, unacceptable toxicity, withdrawal of consent by the patient, discontinuation by the physician, or study completion or termination. Best supportive care was determined by local clinical practice. Crossover between treatment groups was not permitted. Treatment interruptions for up to 14 days and up to two permanent dose reductions were permitted to manage toxicities. Details on dose modifications are provided in the appendix (p 9).

Tumour response was assessed locally according to RECIST (version 1.1)[13] by investigators at screening and every 8 weeks (plus or minus 1 week) until radiographical disease progression (or clinical progression for patients who were treated beyond disease progression), withdrawal of consent, study completion, new anticancer treatment, or death, whichever occurred first. Adverse events were collected throughout the study from the time the informed consent form was signed until 37 days after the last study treatment dose or start of a new anti-tumour treatment, whichever occurred first. Adverse events were coded according to MedDRA (version 25.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).[14] Safety data were reviewed approximately every 6 months by an independent data monitoring committee. The committee was also responsible for evaluating efficacy data at the time of the prespecified non-binding futility analysis of overall survival after approximately one-third of expected deaths had occurred. The independent data monitoring committee consisted of five independent clinical oncology physicians and one independent voting statistician with no conflicts of interest with the study funder. An unmasked statistician from the contract research organisation conducted the analyses for the committee and shared the results with the committee for discussion during the closed sessions of the independent data monitoring committee meetings, and was not a voting member during the committee's decision making. The funder was masked for all the independent data monitoring committee-relevant activities; thus, operational bias was minimised. In total, three meetings (two scheduled safety review meetings and one futility analysis meeting) were held during the conduct of the study before the primary analysis database lock. Details on the

Department of Oncology, CHU UCL Namur, Site Godinne, Yvoir, Belgium (L Faugeras MD); **Department of Medical Oncology, West German Cancer Center, University Hospital Essen, Essen, Germany** (Prof S Kasper MD); **University Hospitals Gasthuisberg, Leuven and KU Leuven, Leuven, Belgium** (Prof E Van Cutsem MD); **Asklepios Tumorzentrum Hamburg, Department of Oncology and Hematology, AK Altona, Hamburg, Germany** (Prof D Arnold MD); **HUTCHMED International Corporation, Florham Park, NJ, USA** (S Nanda MS, Z Yang PhD, W R Schelman MD, M Kania MD); **Vall d'Hebron Barcelona Hospital Campus, Vall d'Hebron Institute of Oncology (VHIO), IOB-Quiron, Barcelona, Spain** (Prof J Tabernero MD); **Division Hematology and Oncology, Vanderbilt-Ingram Cancer Center, Nashville, TN, USA** (Prof C Eng MD)

Correspondence to:
Dr Arvind Dasari, Department of Gastrointestinal Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA
adasari@mdanderson.org

See **Online** for appendix

independent data monitoring committee, including its objectives, composition, scope, frequency, membership, and governance, are outlined in an independent data monitoring committee charter (appendix pp 504–41).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause.

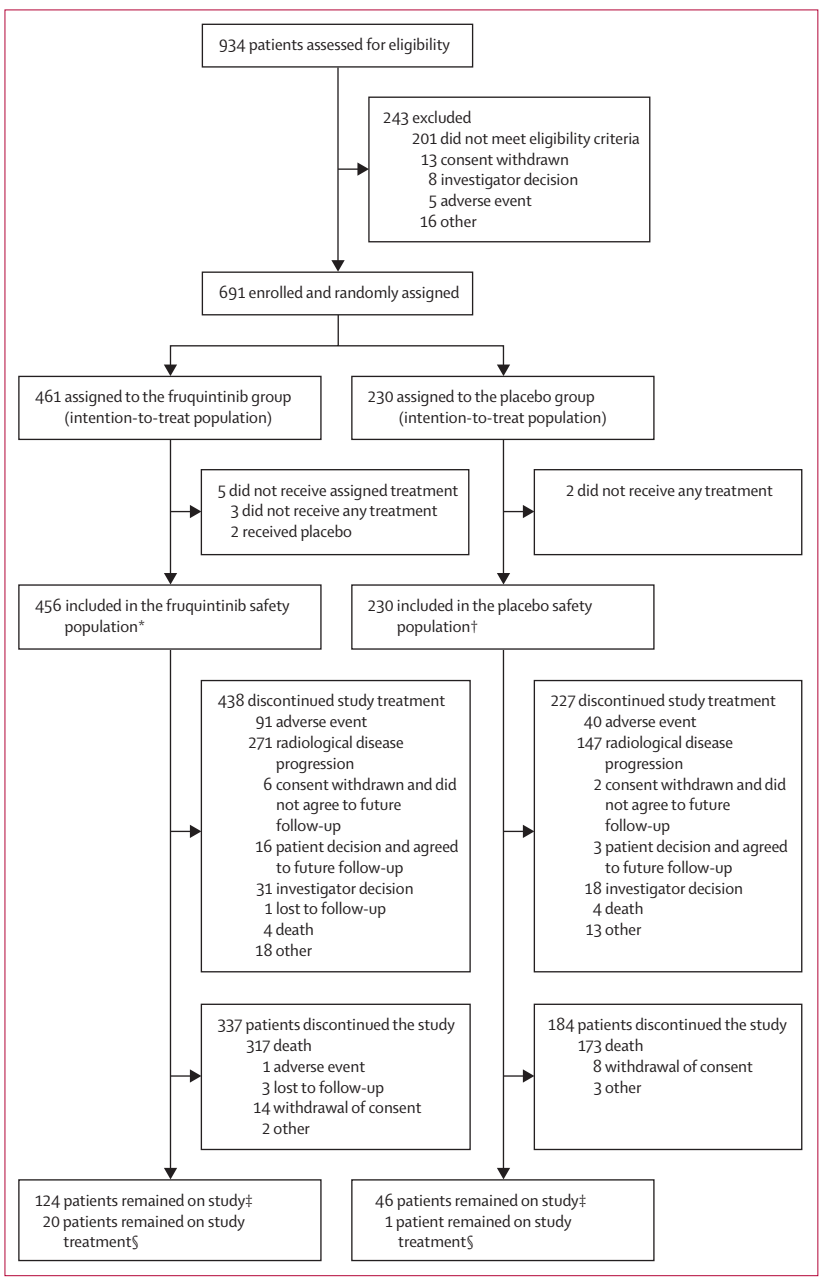


Figure 1: **Study profile**

*Patients who were assigned fruquintinib and received fruquintinib. †Patients who received placebo (including two from the fruquintinib group). ‡Patients with missing end-of-study information were considered to be remaining on study. §Patients who received study drug but had missing end-of-treatment information were considered to be remaining on treatment.

Progression-free survival was a key secondary endpoint, defined as the time from randomisation to the first documentation of disease progression as assessed by the investigator according to RECIST (version 1.1) or death from any cause, whichever occurred first. Other secondary endpoints reported here were objective response rate (proportion of patients with a best overall response of confirmed complete response or partial response), disease control rate (proportion of patients with a best overall response of confirmed complete response, partial response, or stable disease for at least 7 weeks), duration of response (time from first occurrence of complete or partial response until date of radiographical disease progression or death, whichever occurred first), and safety, inclusive of adverse events. Additional secondary endpoints were health-related quality of life per the European Organisation for Research and Treatment of Cancer QLQ-C30 and EQ-5D-5L questionnaires, health-care resource utilisation, and population pharmacokinetics and pharmacodynamics; analyses of these endpoints will be reported elsewhere.

Statistical analysis

Assuming a 10% yearly dropout rate, it was estimated that a total of 480 deaths following randomisation of 687 patients in a 2:1 ratio would provide 90% power (at a two-sided type I error rate of 5%) to show a difference in overall survival between the fruquintinib group and placebo group, with a target HR of 0·73. This translated to a 1·8-month benefit in the median overall survival in the fruquintinib group over the 5 months expected in the placebo group if overall survival was exponentially distributed. A prespecified non-binding futility analysis using an O'Brien-Fleming boundary for overall survival was planned when approximately 160 deaths had occurred. The recommended stopping boundary for futility was a one-sided p value from a stratified log-rank test of at least 0·772 (corresponding to an observed HR of 1·133). Although there were no plans to stop the study early for efficacy based on the overall survival results, a fraction of α (0·0001) was spent as a penalty for the non-binding interim futility analysis. Details on the futility stopping rules are provided in the appendix (p 10), as well as the futility analysis results from overall survival (appendix p 11). Sample size was calculated using East software (version 6.5). To maintain the overall two-sided type I error rate of 5%, the analyses for the primary endpoint and the key secondary endpoint were protected using a fixed-sequence procedure (appendix p 499). The study was originally planned to enrol 522 patients based on a statistical power of 80%. At the very early stage of the study, the protocol was amended to increase the power from 80% to 90%. All other study design parameters remained the same. The decision was made in a masked manner; hence, the overall integrity of the study was properly maintained.

	Fruquintinib group (n=461)	Placebo group (n=230)
Age, years		
Median	64 (56–70)	64 (56–69)
≥65	214 (46%)	111 (48%)
Sex		
Female	216 (47%)	90 (39%)
Male	245 (53%)	140 (61%)
Race		
White	367 (80%)	192 (83%)
Asian	43 (9%)	18 (8%)
Black or African American	13 (3%)	7 (3%)
Other	38 (8%)	13 (6%)
Ethnicity		
Hispanic or Latino	20 (4%)	14 (6%)
Not Hispanic or Latino	405 (88%)	202 (88%)
Not reported or unknown	36 (8%)	14 (6%)
Region		
North America	82 (18%)	42 (18%)
Europe	329 (71%)	166 (72%)
Japan	40 (9%)	16 (7%)
Australia	10 (2%)	6 (3%)
ECOG performance status score*		
0	196 (43%)	102 (44%)
1	265 (57%)	128 (56%)
Primary site at first diagnosis		
Colon left	192 (42%)	92 (40%)
Colon right	97 (21%)	53 (23%)
Colon left and right	4 (1%)	2 (1%)
Colon unknown	25 (5%)	13 (6%)
Rectum	143 (31%)	70 (30%)
Liver metastases		
Yes	339 (74%)	156 (68%)
No	122 (26%)	74 (32%)
Duration of metastatic disease, months†		
≤18	37 (8%)	13 (6%)
>18	424 (92%)	217 (94%)
***RAS* status**		
Wild type	170 (37%)	85 (37%)
Mutant	291 (63%)	145 (63%)
***BRAF V600E* mutation**		
No	401 (87%)	198 (86%)
Yes	7 (2%)	10 (4%)
Other or unknown	53 (11%)	22 (10%)
Microsatellite or mismatch repair status		
MSS or pMMR	427 (93%)	215 (93%)
MSI-H or dMMR	5 (1%)	4 (2%)
Unknown	29 (6%)	11 (5%)

(Table 1 continues in next column)

(Continued from previous column)

	Fruquintinib group (n=461)	Placebo group (n=230)
Number of previous treatment lines in metastatic disease		
Median	4 (3–6)	4 (3–6)
≤3	125 (27%)	64 (28%)
>3	336 (73%)	166 (72%)
Previous therapies		
VEGF inhibitor	445 (97%)	221 (96%)
EGFR inhibitor	180 (39%)	88 (38%)
Immune checkpoint inhibitor	21 (5%)	11 (5%)
BRAF inhibitor	9 (2%)	7 (3%)
Previous trifluridine–tipiracil or regorafenib		
Trifluridine–tipiracil	240 (52%)	121 (53%)
Regorafenib	40 (9%)	18 (8%)
Both	181 (39%)	91 (40%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. MSS=microsatellite stable. pMMR=proficient mismatch repair. MSI-H=microsatellite instability-high. dMMR=deficient mismatch repair. VEGF=vascular endothelial growth factor. EGFR=epidermal growth factor receptor. *ECOG performance status scores range from 0 to 5, with 0 indicating fully active and higher scores indicating greater disability. †Duration of metastatic disease=(date of randomisation – date of diagnosis of metastatic disease)/30·4375.

Table 1: **Baseline characteristics in the intention-to-treat population**

Efficacy endpoints were evaluated in the intention-to-treat population, which included all patients who had been randomly assigned to a treatment group. For time-to-event endpoints, the Kaplan-Meier method was used to estimate the median time and 95% CI. Treatment group difference was tested using the stratified log-rank test to account for the randomisation stratification factors. Stratified HRs and 95% CIs were estimated using a stratified Cox proportional hazards model with the treatment group as the only covariate. The proportional hazards assumption of overall survival and progression-free survival were examined using log–log survival plots. A non-binding futility analysis was done when the first 160 overall survival events had occurred. Specifically, for the futility analysis, all patients available at the time of the futility analysis were included; the first 160 deaths were considered as events and the remaining patients were censored at the date of last known alive date. The analysis was based on the data cutoff date of Sept 24, 2021, by which time 591 patients had been randomly assigned. Although there was a non-binding futility analysis with no plan to stop the study for efficacy, the bias-adjusted statistical inference was not conducted. Prespecified sensitivity and subgroup analyses were done to assess the robustness and consistency of results for the primary analysis of overall survival and progression-free survival. For the objective response rate and disease control rate within a treatment group, the Clopper-Pearson method was used to estimate the response rate with its 95% CIs, and the treatment group comparisons were done using the stratified Cochran-Mantel-Haenszel method to account for the randomisation schedule of stratification factors. Safety evaluations were performed in the safety population, which included all patients who had received at least one dose of fruquintinib or placebo.

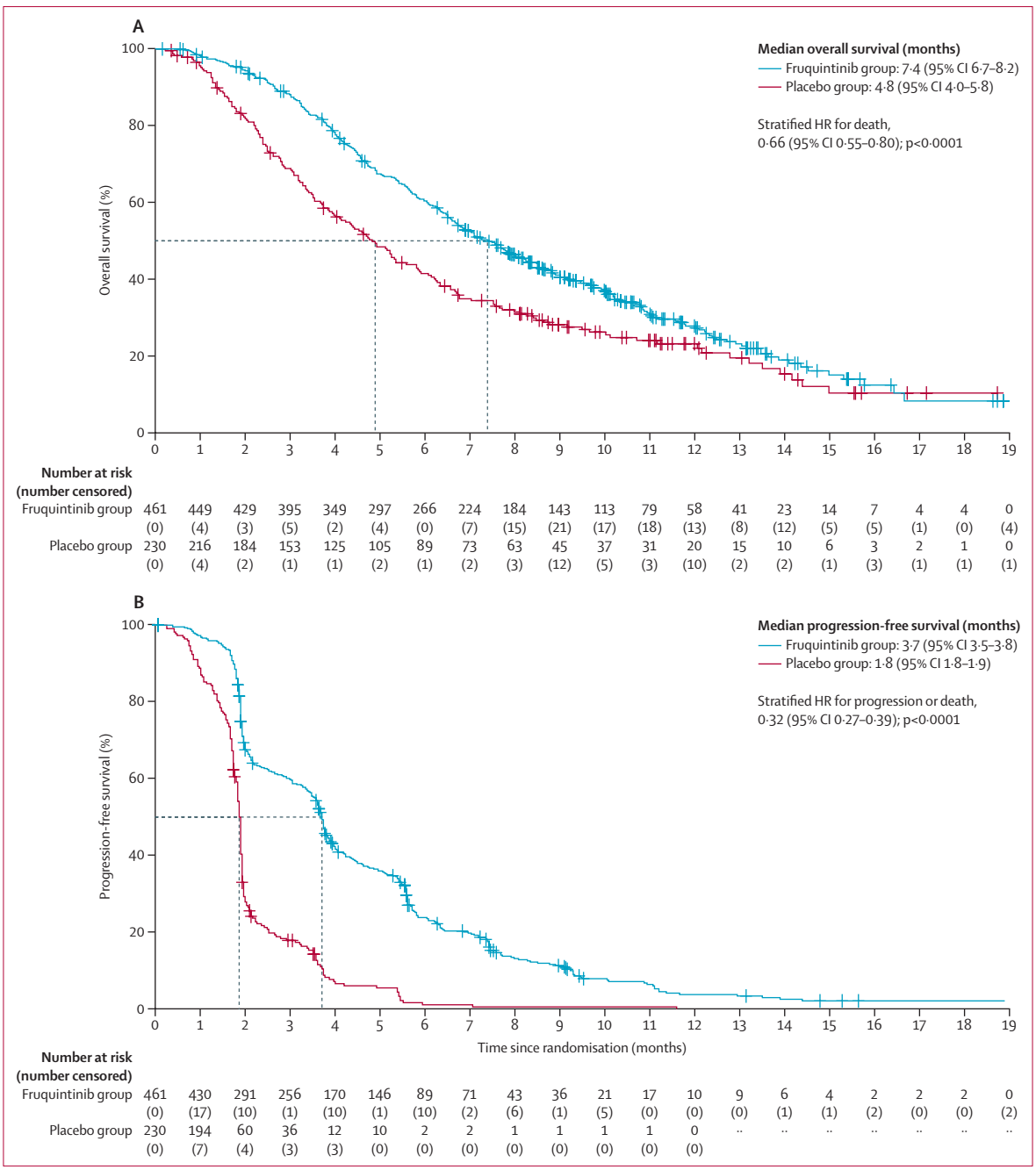


Figure 2: **Kaplan–Meier estimates of overall survival (A) and progression-free survival (B) in the intention-to-treat population**
Ticks show censored patients. HR=hazard ratio.

SAS (version 9.4) was used for all statistical analyses. This study is registered with ClinicalTrials.gov, NCT04322539, and EudraCT, 2020-000158-88, and is ongoing but not recruiting.

Role of the funding source

The funder of the study and steering committee members designed the study. The funder also contributed to data collection, data analysis, data interpretation, and manuscript review and approval. The funder provided financial support for medical writing assistance.

Results

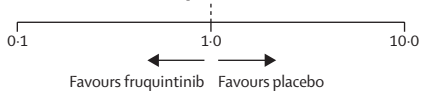
Between Aug 12, 2020, and Dec 2, 2021, 934 patients were assessed for eligibility and 691 were enrolled and randomly assigned to receive fruquintinib (n=461) or placebo (n=230) and included in the intention-to-treat population

(figure 1). Treatment was initiated in 686 patients; 456 patients received fruquintinib and 230 patients received placebo and were included in the safety population. As of June 24, 2022 (data cutoff), 20 (4%) of 461 patients in the fruquintinib group and one (<1%) of 230 in the placebo group remained on treatment.

Baseline demographics and disease characteristics were well balanced between the treatment groups (table 1). In the overall population, the median age was 64 years (IQR 56–70); 436 (63%) of 691 patients had a tumour with *RAS* mutation, and 495 (72%) had liver metastases. The median number of previous lines of

A

	Events/patients		Median overall survival (months)		HR (95% CI)
	Fruquintinib group	Placebo group	Fruquintinib group	Placebo group	
Intention-to-treat population	**317/461**	**173/230**	**7·4**	**4·8**	**0·662 (0·549–0·800)**
Age (years)					
<65	171/247	89/119	7·3	5·2	0·694 (0·534–0·903)
≥65	146/214	84/111	7·6	4·6	0·648 (0·494–0·851)
Sex					
Female	149/216	61/90	7·6	5·8	0·828 (0·609–1·125)
Male	168/245	112/140	7·1	4·6	0·584 (0·456–0·749)
ECOG performance status score					
0	121/196	67/102	9·5	6·8	0·775 (0·573–1·050)
1	196/265	106/128	6·0	3·7	0·571 (0·449–0·728)
Race					
White	260/367	145/192	7·6	4·8	0·696 (0·567–0·854)
Asian	24/43	14/18	7·1	4·7	0·377 (0·171–0·833)
African American	7/13	5/7	8·2	2·0	0·550 (0·135–2·231)
Other	26/38	9/13	6·8	7·7	1·199 (0·478–3·008)
Region					
North America	50/82	29/42	7·6	6·1	0·620 (0·387–0·995)
Europe	237/329	130/166	7·6	4·6	0·688 (0·554–0·855)
Asia Pacific	30/50	14/22	6·9	5·8	0·631 (0·321–1·241)
Duration of metastatic disease (months)					
≤18	30/37	8/13	4·7	2·8	0·605 (0·260–1·406)
>18	287/424	165/217	7·6	4·9	0·642 (0·529–0·779)
Primary tumour location at diagnosis					
Colon	195/279	109/137	7·0	4·6	0·672 (0·528–0·855)
Rectum	99/143	49/70	7·8	5·2	0·633 (0·446–0·900)
Colon and rectum	23/39	15/23	9·9	6·6	0·686 (0·339–1·388)
***RAS* status**					
Wild type	119/170	62/85	7·7	4·4	0·667 (0·489–0·909)
Mutant	198/291	111/145	7·1	5·1	0·683 (0·539–0·865)
Previous treatment lines for metastatic disease					
≤3	80/125	45/64	7·6	5·2	0·714 (0·488–1·043)
>3	237/336	128/166	7·1	4·6	0·645 (0·519–0·802)
Previous VEGF inhibitors					
Yes	306/445	167/221	7·4	4·9	0·683 (0·565–0·827)
No	11/16	6/9	10·0	3·5	0·193 (0·024–1·557)
Previous EGFR inhibitors					
Yes	127/180	64/88	7·4	4·4	0·689 (0·507–0·936)
No	190/281	109/142	7·5	5·1	0·666 (0·524–0·846)
Previous trifluridine–tipiracil or regorafenib					
Trifluridine–tipiracil	165/240	88/121	7·7	5·1	0·723 (0·557–0·938)
Regorafenib	25/40	12/18	10·2	8·2	0·772 (0·379–1·573)
Both	127/181	73/91	6·8	4·4	0·600 (0·447–0·805)
Liver metastases					
Yes	255/339	132/156	6·4	3·7	0·576 (0·465–0·713)
No	62/122	41/74	12·1	8·4	0·771 (0·513–1·158)



(Figure 3 continues on next page)

therapy for metastatic disease was 4 (IQR 3–6); 502 (73%) patients had received more than 3 previous lines of therapy for metastatic disease. Overall, 666 (96%) patients had received previous anti-VEGF therapy and 268 (39%) had received previous anti-EGFR therapy; all patients had received previous treatment with either trifluridine–tipiracil (n=361 [52%]), regorafenib (n=58 [8%]), or both (n=272 [39%]; table 1).

B

	Events/patients		Median progression-free survival (months)		HR (95% CI)
	Fruquintinib group	Placebo group	Fruquintinib group	Placebo group	
Intention-to-treat population	**392/461**	**213/230**	**3·7**	**1·8**	**0·321 (0·267–0·386)**
Age (years)					
<65	214/247	111/119	3·7	1·9	0·329 (0·255–0·424)
≥65	178/214	102/111	3·7	1·8	0·314 (0·241–0·410)
Sex					
Female	190/216	81/90	3·7	1·8	0·351 (0·263–0·468)
Male	202/245	132/140	3·7	1·9	0·302 (0·237–0·385)
ECOG performance status score					
0	169/196	90/102	3·8	1·9	0·264 (0·197–0·354)
1	223/265	123/128	3·4	1·8	0·351 (0·277–0·446)
Race					
White	312/367	176/192	3·7	1·9	0·313 (0·255–0·383)
Asian	37/43	17/18	3·6	1·7	0·286 (0·140–0·584)
African American	9/13	7/7	2·5	1·7	0·081 (0·014–0·468)
Other	34/38	13/13	3·4	1·9	0·525 (0·248–1·110)
Region					
North America	64/82	36/42	3·7	1·7	0·261 (0·163–0·417)
Europe	283/329	158/166	3·7	1·9	0·324 (0·261–0·401)
Asia Pacific	45/50	19/22	3·6	1·7	0·271 (0·144–0·509)
Duration of metastatic disease (months)					
≤18	35/37	11/13	1·9	1·8	0·361 (0·166–0·787)
>18	357/424	202/217	3·7	1·8	0·300 (0·249–0·363)
Primary tumour location at diagnosis					
Colon	241/279	127/137	3·6	1·8	0·294 (0·231–0·375)
Rectum	118/143	64/70	3·9	1·9	0·315 (0·225–0·441)
Colon and rectum	33/39	22/23	3·5	1·9	0·386 (0·202–0·739)
***RAS* status**					
Wild type	145/170	76/85	3·7	1·9	0·333 (0·245–0·454)
Mutant	247/291	137/145	3·6	1·8	0·318 (0·254–0·399)
Previous treatment lines for metastatic disease					
≤3	108/125	57/64	3·5	1·9	0·280 (0·192–0·409)
>3	284/336	156/166	3·7	1·8	0·334 (0·270–0·412)
Previous VEGF inhibitors					
Yes	377/445	206/221	3·7	1·9	0·335 (0·278–0·402)
No	15/16	7/9	5·9	1·6	0·020 (0·001–0·385)
Previous EGFR inhibitors					
Yes	154/180	79/88	3·7	1·9	0·325 (0·239–0·440)
No	238/281	134/142	3·7	1·8	0·310 (0·247–0·391)
Previous trifluridine–tipiracil or regorafenib					
Trifluridine–tipiracil	210/240	111/121	3·6	1·9	0·367 (0·287–0·470)
Regorafenib	29/40	16/18	3·6	1·9	0·292 (0·139–0·611)
Both	153/181	86/91	3·7	1·8	0·285 (0·212–0·382)
Liver metastases					
Yes	297/339	149/156	3·6	1·8	0·291 (0·234–0·362)
No	95/122	64/74	4·5	1·9	0·334 (0·235–0·476)

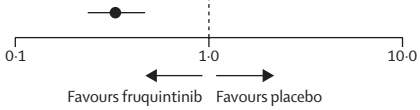


Figure 3: **Key subgroup analysis of overall survival (A) and progression-free survival (B) in the intention-to-treat population**
Error bars show 95% CIs. Asia-Pacific region includes Japan and Australia. ECOG=Eastern Cooperative Oncology Group. EGFR=epidermal growth factor receptor. HR=hazard ratio. VEGF=vascular endothelial growth factor.

The median duration of treatment exposure was 3·1 months (IQR 1·8–5·6; mean 4·0 months [SD 3·1]) for fruquintinib and 1·8 months (IQR 1·0–2·3; mean 2·0 months [SD 1·3]) for placebo. The median number of treatment cycles was 3·0 (IQR 2·0–6·0) for fruquintinib and 2·0 (1·0–3·0) for placebo; 223 (49%) of 461 patients in the fruquintinib group received four or more treatment cycles versus 34 (15%) of 230 in the placebo group. The median relative dose intensity was 92% in the fruquintinib group and 98% in the placebo group (appendix p 12). After study treatment ended, 134 (29%) patients in the fruquintinib group and 79 (34%) in the placebo group received additional treatment during survival follow-up (appendix p 13). 22 (3%) of 691 patients were excluded from the per-protocol analysis population as these patients had protocol deviations that could have affected overall survival or tumour assessment-related efficacy endpoints; the excluded patients were balanced between the groups, with 17 (4%) patients in the fruquintinib group and five (3%) in the placebo group (appendix p 17).

The primary analysis was done after 490 (71%) of 691 patients had died: 317 (69%) in the fruquintinib group and 173 (75%) in the placebo group. Loss to follow-up or withdrawal of consent was low, occurring in 17 (4%) patients in the fruquintinib group and eight (3%) in the placebo group. Median follow-up was 11·3 months (IQR 9·0–14·2) in the fruquintinib group and 11·2 months (8·7–15·5) in the placebo group. Median overall survival was 7·4 months (95% CI 6·7–8·2) in the fruquintinib group versus 4·8 months (4·0–5·8) in the placebo group (absolute difference 2·6 months; HR 0·66, 95% CI 0·55–0·80; p<0·0001; figure 2A). The Kaplan-Meier plot for overall survival showed an early separation of the curves in favour of the fruquintinib group, which was maintained over the duration of the study. The visual assessment of log–log survival curves indicated the curves were reasonably parallel between the two groups, with some convergence towards the later part of the curves; however, this should not affect the validity and interpretability of the HR. The proportion of patients who were still alive at 9 months was 41% (95% CI 36–46) in the fruquintinib group and 28% (22–34) in the placebo group.

A total of 605 (88%) of 691 patients had disease progression or died: 392 (85%) in the fruquintinib group and 213 (93%) in the placebo group. Median progression-free survival was 3·7 months (95% CI 3·5–3·8) in the fruquintinib group versus 1·8 months (1·8–1·9) in the placebo group (absolute difference 1·9 months; HR 0·32, 95% CI 0·27–0·39; p<0·0001; figure 2B). For progression-free survival, there was no violation of the proportional hazards assumption.

Subgroup analyses of overall survival and progression-free survival showed results that were consistent with the benefit observed in the intention-to-treat population across nearly all prespecified subgroups, including by randomisation stratification factors: previous therapy with trifluridine–tipiracil or regorafenib, *RAS* mutation status, and duration of metastatic disease (figure 3).

	Fruquintinib group (n=461)	Placebo group (n=230)	Treatment effect	Two-sided p value
Time-to-event endpoints				
Overall survival, months	7·4 (6·7–8·2)	4·8 (4·0–5·8)	0·66 (0·55–0·80)	<0·0001
Progression-free survival, months	3·7 (3·5–3·8)	1·8 (1·8–1·9)	0·32 (0·27–0·39)	<0·0001
Antitumour activity endpoints				
Best overall response*				
Complete response	0	0	..	..
Partial response	7 (2%)	0	..	..
Stable disease	249 (54%)	37 (16%)	..	..
Progressive disease	139 (30%)	143 (62%)	..	..
Not evaluable	6 (1%)	1 (<1%)	..	..
NA†	60 (13%)	49 (21%)	..	..
Objective response rate	7 (2%, 0·6–3·1)	0 (0%, 0·0–1·6)	2% (0·4–2·7)	0·059
Disease control rate	256 (56%, 50·9–60·1)	37 (16%, 11·6–21·5)	39%‡ (32·8–46·0)	<0·0001
Duration of response, months				
Median	10·7 (3·9–NE)	0 (NA)	..	..
Range	2·1–16·9§	NA	..	..

Data are n (%), n (%, 95% CI), or median (95% CI) unless otherwise stated. Treatment effect is hazard ratio (95% CI) for time-to-event endpoints and adjusted difference (95% CI) for antitumour activity endpoints. NA=not applicable. NE=not estimable. *The denominators for the percentages are patients in the intention-to-treat population, which included all patients who were randomly assigned to a study group; patients who could not be evaluated, who had no assessment available, or who did not start either therapy were not excluded from this analysis. †This category included patients who had no baseline or postbaseline imaging. ‡Percentage reflects adjusted difference before rounding in each group. §The Kaplan-Meier method for censored data was used to calculate duration.

Table 2: **Efficacy endpoints in the intention-to-treat population**

Investigator-assessed objective response was documented in seven (2%) of 461 patients in the fruquintinib group compared with none in the placebo group (adjusted difference 2%, 95% CI 0·4–2·7; p=0·059; table 2). No complete responses were observed. The median duration of response in the fruquintinib group was 10·7 months (95% CI 3·9–not estimable); maximum duration of response was ongoing at greater than 16·9 months. The disease control rate was 56% (256 of 461 patients) in the fruquintinib group compared with 16% (37 of 230) in the placebo group (adjusted difference 39%, 95% CI 32·8–46·0; p<0·0001).

Overall, 451 (99%) of 456 patients in the fruquintinib group and 213 (93%) of 230 in the placebo group had at least one adverse event (table 3). The most frequent adverse events of any grade, regardless of causality, were hypertension (168 [37%] patients in the fruquintinib group *vs* 20 [9%] in the placebo group) and asthenia (155 [34%] *vs* 52 [23%]). Grade 3 or worse adverse events occurred in 286 (63%) patients who received fruquintinib compared with 116 (50%) who received placebo; the most frequent of these events were hypertension (62 [14%] patients in the fruquintinib group *vs* two [1%] in the placebo group), asthenia (35 [8%] *vs* nine [4%]), and hand-foot syndrome (29 [6%] *vs* none). The incidence of serious adverse events was similar between groups.

	Fruquintinib group (n=456)		Placebo group (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
At least one adverse event				
Any	451 (99%)	286 (63%)	213 (93%)	116 (50%)
Hypertension	168 (37%)	62 (14%)	20 (9%)	2 (1%)
Asthenia	155 (34%)	35 (8%)	52 (23%)	9 (4%)
Decreased appetite	124 (27%)	11 (2%)	40 (17%)	3 (1%)
Diarrhoea	110 (24%)	16 (4%)	24 (10%)	0
Hypothyroidism	94 (21%)	2 (<1%)	1 (<1%)	0
Fatigue	91 (20%)	18 (4%)	37 (16%)	2 (1%)
Hand-foot syndrome	88 (19%)	29 (6%)	6 (3%)	0
Abdominal pain	83 (18%)	14 (3%)	37 (16%)	7 (3%)
Nausea	79 (17%)	3 (1%)	42 (18%)	2 (1%)
Proteinuria	79 (17%)	8 (2%)	12 (5%)	2 (1%)
Constipation	78 (17%)	2 (<1%)	22 (10%)	0
Dysphonia	74 (16%)	0	12 (5%)	0
Stomatitis	67 (15%)	8 (2%)	8 (3%)	1 (<1%)
Vomiting	66 (14%)	7 (2%)	28 (12%)	4 (2%)
Mucosal inflammation	62 (14%)	2 (<1%)	6 (3%)	0
Weight decrease	56 (12%)	3 (1%)	21 (9%)	1 (<1%)
Arthralgia	50 (11%)	4 (1%)	10 (4%)	0
Aspartate aminotransferase increase	48 (11%)	10 (2%)	11 (5%)	3 (1%)
Alanine aminotransferase increase	47 (10%)	14 (3%)	9 (4%)	1 (<1%)
Back pain	47 (10%)	6 (1%)	17 (7%)	3 (1%)
Pyrexia	46 (10%)	2 (<1%)	23 (10%)	0
Serious adverse events				
Any	172 (38%)	163 (36%)†	88 (38%)	85 (37%)†
Adverse events leading to death‡				
Any	49 (11%)	49 (11%)	45 (20%)	45 (20%)
Adverse events of special interest				
Any	368 (81%)	169 (37%)§	122 (53%)	44 (19%)§
Hypertension	175 (38%)	64 (14%)	20 (9%)	2 (1%)
Dermatological toxicity	157 (34%)	31 (7%)	27 (12%)	1 (<1%)
Thyroid dysfunction	123 (27%)	2 (<1%)	4 (2%)	0
Hepatic function abnormal	113 (25%)	38 (8%)	44 (19%)	21 (9%)
Infection	96 (21%)	30 (7%)	29 (13%)	13 (6%)
Proteinuria	80 (18%)	8 (2%)	12 (5%)	2 (1%)
Haemorrhage	65 (14%)	8 (2%)	22 (10%)	4 (2%)
Embolic and thrombotic events	21 (5%)	14 (3%)	5 (2%)	2 (1%)
Gastrointestinal perforation	16 (4%)	10 (2%)	1 (<1%)	1 (<1%)
Left ventricular ejection fraction decrease	5 (1%)	4 (1%)	6 (3%)	2 (1%)

Data are n (%). Listed are adverse events of any grade that occurred in at least 10% of patients, grade 3 or worse events that occurred among these events, and adverse events of special interest by category. *Of five patients assigned to the fruquintinib group, three did not receive fruquintinib treatment, and two patients received placebo instead; in the placebo group, two patients did not receive treatment. †Most frequent (≥2%) grade 3 or worse serious adverse events with fruquintinib compared with placebo were pneumonia (2% *vs* <1%) and abdominal pain (2% *vs* 1%). ‡Disease progression was the most frequently reported term leading to death in each group (7% in the fruquintinib group and 13% in the placebo group). §Most frequent (>5%) grade 3 or worse adverse events of special interest with fruquintinib compared with placebo were hypertension (14% *vs* 1%) and hand-foot syndrome (incorporated in dermatological toxicity; 6% *vs* 0%).

Table 3: **Adverse events in the safety population***

Adverse events led to death in 49 (11%) patients who received fruquintinib and 45 (20%) who received placebo, with disease progression as the most frequently reported term in each group (31 [7%] *vs* 30 [13%]); one patient receiving placebo died from COVID-19 (table 3). There was one treatment-related death in each group (intestinal perforation in the fruquintinib group and cardiac arrest in the placebo group; appendix p 17).

Dose interruptions due to adverse events occurred in 213 (47%) of 456 patients who received fruquintinib and 61 (27%) of 230 who received placebo. Dose reductions due to adverse events occurred in 110 (24%) patients who received fruquintinib and nine (4%) who recieved placebo (appendix p 17); the most frequent adverse events leading to dose reduction with fruquintinib were hand-foot syndrome (24 [5%] of 456 patients), hypertension (17 [4%]), and asthenia (16 [4%]; appendix p 18). Overall, 93 (20%) patients who received fruquintinib and 49 (21%) who received placebo discontinued treatment due to adverse events; asthenia was the most frequent reason for fruquintinib discontinuation (seven [2%]; appendix pp 17–18).

Discussion

This international, phase 3 study met its primary and key secondary endpoints, showing significant improvements in overall survival and progression-free survival with fruquintinib in a heavily pretreated patient population with refractory metastatic colorectal cancer. The benefit of fruquintinib over placebo was evident by the 34% reduction in risk of death and 68% reduction in risk of disease progression or death. At 6 months, 24% of patients in the fruquintinib group versus 1% in the placebo group had progression-free survival. The overall survival improvement seen with fruquintinib is further supported by the findings in the placebo group, which were similar to previous studies in metastatic colorectal cancer.[5,6,15] Furthermore, a disease control rate of 56% is notable considering the more heavily pretreated patient population in FRESCO-2 relative to previous studies of fruquintinib[10] and other therapies[5,6] for metastatic colorectal cancer.

Fruquintinib was well tolerated in this heavily pretreated patient population. Patients who received fruquintinib stayed on treatment for almost twice as long as those who received placebo (median 3·1 months *vs* 1·8 months), consistent with favourable efficacy and tolerability of fruquintinib. Nearly half of patients assigned to fruquintinib received four or more cycles, with a 92% median relative dose intensity. The safety data reported here were consistent with the safety profile established from previous reports.[10,11] Although grade 3 or worse adverse events occurred in 63% of patients in the fruquintinib group compared with 50% in the placebo group, most adverse events, including hypertension, asthenia, and hand-foot syndrome, could be managed with supportive care and dose modification. Dose interruption occurred in 47% of patients and dose reductions occurred in 24% of patients, which compares favourably with regorafenib[6] and is encouraging, considering the later-line setting of these patients. A

similar proportion of patients in the fruquintinib and placebo groups discontinued treatment due to adverse events (20% *vs* 21%). The discontinuation rates observed here are likely to reflect the refractory patient population in this study.

Overall survival and progression-free survival benefits with fruquintinib were observed across nearly all prespecified subgroups, including those with poor prognostic factors. Notably, benefits with fruquintinib were seen regardless of previous therapy, including previous treatment with trifluridine–tipiracil (>90% of patients) or regorafenib. These results are particularly relevant given that 48% of patients had received previous treatment with regorafenib, and suggest that inhibition of the VEGF pathway remains an important mechanism of disease control even in later-line settings. The higher target selectivity of fruquintinib compared with other approved anti-VEGF or anti-VEGFR therapies[7,16,17] could explain the efficacy benefit observed in patients treated with fruquintinib, regardless of previous exposure to regorafenib.

Overall survival and progression-free survival benefits were also consistent regardless of number of previous lines of therapy for metastatic disease. These data support the efficacy and tolerability of fruquintinib in heavily pretreated patients (73% of the FRESCO-2 population had received more than 3 previous lines of therapy for metastatic disease) as well as the efficacy of fruquintinib in earlier lines of therapy (27% of patients had received ≤3 previous lines of therapy for metastatic disease). Consistent with these latter results, the activity of fruquintinib has previously been shown in patients without extensive previous anti-VEGF, trifluridine–tipiracil, or regorafenib treatment.[10,11]

Since the inception of this trial, there were advances in the therapeutic landscape for metastatic colorectal cancer that have targeted specific, small subpopulations of patients with alterations such as *KRAS G12C* and *HER2*. Likewise, the phase 3 SUNLIGHT trial[18] evaluated the role of trifluridine–tipiracil with or without bevacizumab in patients following two previous lines of therapy in metastatic colorectal cancer; nearly 24% of the patients had not received a previous anti-VEGF agent, reflecting the earlier-line setting in which it was conducted. Patients in FRESCO-2 were required to have received previous treatment with targeted therapies where approved and available in participating countries. Moreover, most patients had received a previous anti-VEGF biologic agent as well as trifluridine–tipiracil or regorafenib. As a result, the primary findings of FRESCO-2 show the efficacy and safety of fruquintinib across a broad patient population and contribute to the body of evidence, including results from the FRESCO study, supporting the clinical benefit of single-agent fruquintinib for patients with refractory metastatic colorectal cancer[10,11,19,20] in multiple settings.

FRESCO-2 was conducted during the COVID-19 pandemic, when institutional participation in clinical studies was limited. Nevertheless, enrolment was completed in less than 17 months, underscoring the high unmet need for treatment options in this population of patients with metastatic colorectal cancer.

A limitation of this study is that the COVID-19 pandemic hindered the completion of blood-based circulating tumour DNA correlative analyses as unanticipated supply chain issues prevented the timely distribution and collection of test kits necessary to collect samples. Although the inability to complete these exploratory analyses prevented a deeper understanding of whom might benefit from fruquintinib, the absence of these data did not affect the primary and secondary endpoint analyses or overall conclusions.

In conclusion, treatment with fruquintinib prolonged overall survival and progression-free survival compared with placebo in heavily pretreated patients with refractory metastatic colorectal cancer from an international population. The significant and clinically meaningful benefit with fruquintinib, the true extent of which will be more clear following analyses of the quality of life assessments, was coupled with a favourable safety profile. Results from FRESCO-2 support fruquintinib as a new oral treatment option globally that will add to the armamentarium for patients with refractory metastatic colorectal cancer, and will enrich the continuum of care for these patients.

Contributors

AD, JTa, TY, **ASo**, EVC, JY, and CE conceptualised and designed the study. ZY, JJ, RG-C, AD, JTa, TY, TS, ASh, SN, AS-B, ASo, LF, EVC, DA, FG, CE, PG-A, SL, JTo, ASP, and AB contributed to the collection and assembly of the data. ZY, FG, JJ, RG-C, AD, JTa, TY, TS, SN, ASo, EVC, DA, JY, MD, FG, CE, PG-A, SL, and MD contributed to the analysis and interpretation of the data. All authors participated in the manuscript development process and provided final approval of the manuscript. All authors had full access to the study data, verified the data, and were responsible for the decision to submit for publication. All authors vouch for the accuracy and thoroughness of the data and for the fidelity of the study to the statistical analysis plan and study protocol.

Declaration of interests

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Data sharing

The study protocol and statistical analysis plan are available in the appendix. De-identified participant data that underlie the results reported in this Article can be made available to investigators for research purposes on a case-by-case basis after the time of this publication. Requests for access to data should be addressed to the HUTCHMED author WRS (williams@hutch-med.com) for consideration.

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