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

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Research in context

Evidence before this study

We searched PubMed for clinical trial articles using ("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") between January 1, 2015, and December 31, 2019. The search yielded 35 results. Studies were reviewed if they were conducted in the third-line or later metastatic colorectal cancer setting and reported primary endpoint results. We identified six relevant randomised phase 3 studies evaluating trifluridine/tipiracil, regorafenib (two studies each), nintedanib (one study), and our previous study of fruquintinib conducted in China (FRESCO).

Trifluridine/tipiracil, an oral chemotherapy, and regorafenib, a multikinase inhibitor, have both shown incremental benefit on 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 VEGFR-1, -2, and -3. In the FRESCO study, fruquintinib demonstrated statistically significant improvement in both overall survival and progression-free survival compared with placebo. However, at the time the study was conducted, treatment patterns for metastatic colorectal cancer in China differed from those in the rest of the world; only one-third of the patients received prior anti-VEGF therapy, and none had received TAS-102 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 a global, randomised, phase 3 study to assess the efficacy and safety of fruquintinib in patients with treatment histories representative of current global treatment practices, which includes treatment with trifluridine/tipiracil and/or regorafenib.

Added value of this study

Patients with surgically unresectable metastatic colorectal cancer have limited treatment options. Trifluridine/tipiracil and regorafenib are both widely approved in previously treated patients with marginal benefit in median overall survival. FRESCO-2 is a multiregional, double-blind, placebo-controlled study of fruquintinib plus best supportive care in patients with metastatic colorectal cancer who have progressed on or were intolerant to all standard-of-care therapies including trifluridine/tipiracil and/or regorafenib. To our knowledge, FRESCO-2 is the first study to show efficacy of an oral VEGFR inhibitor in previously treated patients with prior trifluridine/tipiracil and/or regorafenib, with a reduction in the overall risk of death by 34% and

in progression or death of 68% compared to placebo. The observed benefits were consistent across nearly all prespecified subgroups, including number of prior lines of therapy for metastatic disease and prior treatment with trifluridine/tipiracil and/or regorafenib. Fruquintinib was also well tolerated with a safety profile consistent with previous reports for its monotherapy.

Implication 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 progressed on or were intolerant to trifluridine/tipiracil and/or regorafenib. Collectively, evidence for fruquintinib supports its use in multiple settings and should be considered as a new global treatment option for patients with chemotherapy-refractory metastatic colorectal cancer in which limited treatment options exist.

Summary

Background Effective systemic therapy options for patients with advanced, chemotherapy-refractory colorectal cancer are limited. We aimed to evaluate the efficacy and safety of fruquintinib, a highly selective and potent oral inhibitor VEGFR-1, -2, and -3 in this patient population.

Methods FRESCO-2 was a global, double-blind, multiregional phase 3 study conducted at 124 sites across 14 countries in patients with metastatic colorectal cancer who had received all current standard approved cytotoxic and targeted therapies and progressed on or were intolerant to trifluridine/tipiracil and/or regorafenib. Eligible patients were randomly assigned (2:1) to receive fruquintinib or matching placebo (5-mg capsules given orally once daily for 3 weeks on, 1 week off, every 28 days) plus best supportive care. Stratification factors were prior trifluridine/tipiracil and/or regorafenib, *RAS* mutation status, and duration of metastatic disease. The primary endpoint was overall survival. A non-binding futility analysis was conducted 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 active but not recruiting.

Findings Between August 12, 2020, and December 2, 2021, 691 patients were randomly assigned to fruquintinib (n=461) or placebo (n=230). Patients had a median of four lines of prior systemic therapy for metastatic disease, and 73% received more than three lines of prior systemic therapy for metastatic disease. The primary and key secondary endpoints were met. Treatment with fruquintinib versus placebo resulted in a statistically significant improvement in overall survival (median, 7·4 months vs 4·8 months; hazard ratio, 0·66; 95% CI 0·55–0·80; p<0·001). Grade ≥3 adverse events occurred in 286 (63%) of 456 patients receiving fruquintinib and 116 (50%) of 230 receiving placebo; those occurring in ≥5% of patients on fruquintinib included hypertension (14%), asthenia (8%), and hand-foot syndrome (6%). There was one treatment-related death per group.

Interpretation Fruquintinib treatment resulted in a statistically significant and clinically meaningful benefit for overall survival versus placebo. These data support fruquintinib as a global treatment option for patients with refractory metastatic colorectal cancer.

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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 will 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 nonselective treatment options include the oral agents trifluridine/tipiracil and the multikinase inhibitor, regorafenib, with incremental effects on median survival.[5,6] Consequently, an unmet need for safe and effective treatments exists for patients with refractory metastatic colorectal cancer.

Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFRs)-1, -2, and -3,[7] key regulators of angiogenesis associated with tumour growth and metastasis.[8,9] In the phase 3 FRESCO study (NCT02314819) conducted in patients with metastatic colorectal cancer who had at least two prior lines of chemotherapy, treatment with fruquintinib resulted in statistically significant improvement in overall survival (median, 9·3 months [95% CI 8·2–10·5] vs 6·6 months [95% CI 5·9–8·1] for placebo; hazard ratio, 0·65 [95% CI 0·51–0·83]; p<0·001) and progression-free survival (median, 3·7 months [95% CI 3·7–4·6] vs 1·8 months [95% CI 1·8–1·8] for placebo; hazard ratio, 0·26 [95% CI 0·21–0·34]; p<0·001).[10] These results led to the approval of fruquintinib in China in 2018. However, when the FRESCO study was conducted, treatment patterns for metastatic colorectal cancer in China differed from the rest of the world; only 30% of patients had received prior treatment with a VEGF inhibitor and 14% had received a prior epidermal growth factor receptor (EGFR) antibody, none had received trifluridine/tipiracil, and those exposed to regorafenib were excluded.[10] An ongoing phase 1/1b expansion cohort study (NCT03251378) of fruquintinib conducted in the United States, which included patients with metastatic colorectal cancer with or without prior trifluridine/tipiracil and/or regorafenib, demonstrated encouraging preliminary antitumour efficacy and safety,[11] further supporting the investigation of fruquintinib in a refractory metastatic colorectal cancer population.

FRESCO-2 was a global phase 3 study investigating the efficacy and safety of fruquintinib versus placebo in patients with heavily pretreated metastatic colorectal cancer who represented current global treatment practices. Here, we report the final efficacy analysis of FRESCO-2.

Methods

Study design and patients

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

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, including the International Council for Harmonisation. The protocol and amendments (available in the appendix pp 132-268) were approved by the institutional review board and independent ethics committee at each participating site. All patients provided written informed consent at enrollment.

Randomisation and masking

Patients were assigned an identification number by an interactive web response system. Eligible patients 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 using randomised blocks based on stratification factors of prior therapy (trifluridine/tipiracil vs regorafenib vs 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 prior regorafenib was limited to 50% of total randomly assigned patients. All patients, investigators, study site personnel, and sponsors in regular contact with the study site, except for selected sponsor pharmacovigilance personnel, were blinded to randomisation assignments and remained blinded throughout the study.

Procedures

Fruquintinib, as a 5-mg capsule or matching placebo, was given orally once daily for 3 weeks on, 1 week off, repeated every 28 days. Treatment continued until disease progression, death, unacceptable toxicity, withdrawal of consent by the patient, discontinuation by the physician, or study completion/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.

Tumour response was assessed locally according to RECIST v1.1[13] by investigators at screening and every 8 weeks (±1 week) until radiographic 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 beginning from the time the informed consent form is signed until 37 days after the last study treatment dose or start of a new antitumour treatment, whichever occurred first. Adverse events were coded according to MedDRA version 25.0 and graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events v5.0.[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. Details on the independent data monitoring committee, including its objectives, composition, scope, frequency, membership, and governance, are outlined in an independent data monitoring committee charter (appendix pp 503-40).

Outcomes

The primary endpoint was overall survival, defined as the time from randomisation to death from any cause. Progression-free survival was a key secondary endpoint, defined as the time from randomisation to the first documentation of disease progression as assessed by investigator according to RECIST v1.1 or death from any cause, whichever occurred first. Other secondary endpoints reported here included objective response rate (proportion of patients with a confirmed complete response or partial response), disease control rate (proportion of patients with a 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 radiographic disease progression or death, whichever occurred first), and safety, inclusive of adverse events. Additional secondary endpoints included health-related quality of life per the European Organisation for Research and Treatment of Cancer QLQ-C30 and EQ-5D-5L questionnaires, healthcare resource utilisation, and population pharmacokinetics and pharmacodynamics; analyses of these endpoints will be reported separately.

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 hazard ratio 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. Details on futility stopping rules are provided in the protocol (pp 211). Sample size was calculated using East® version 6.5 software. 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 498). The study was originally planned to enroll 522 patients based on a statistical power of 80%. At the very early stage of the study conduct, 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 blinded manner; hence, the overall integrity of the study was properly maintained.

Efficacy endpoints were evaluated in the intention-to-treat population, which included all patients who had undergone randomisation. For time-to-event endpoints, the Kaplan–Meier method was used to estimate the median time and its 95% CI. Treatment group difference was tested using the stratified log-rank test to account for the randomisation stratification factors. Stratified hazard ratios and 95% CIs were estimated using a stratified Cox proportional-hazards model with the treatment group as the only covariate. The proportional-hazard assumption of overall survival and progression-free survival were examined using log-log survival plots. Although there was a non-binding futility analysis, the bias-adjusted statistical inference was not conducted because there was no plan to stop the study for efficacy. Prespecified sensitivity and subgroup analyses were performed 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 along with its 95% CIs, and the treatment group comparisons were conducted 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.

SAS (version 9·4) was used for all statistical analyses. This study is registered with ClinicalTrials.gov, NCT04322539 and EudraCT, 2020-000158-88.

Role of the funding source

The funder of the study and steering committee members designed the study. The funder also contributed to data collection, analysis, and interpretation as well as manuscript review and approval. The funder provided financial support for medical writing assistance. All authors edited and revised manuscript drafts and approved the final version.

Results

Between August 12, 2020, and December 2, 2021, a total of 934 patients across 14 countries were screened; 691 patients were randomly assigned to receive treatment, with 461 patients assigned to fruquintinib and 230 patients assigned to placebo (intention-to-treat population). Treatment was initiated in 686 patients; 456 patients received fruquintinib and 230 patients received placebo (safety-analysis population). As of June 24, 2022 (data cutoff), 20 patients (4%) in the fruquintinib group and one patient (<1%) in the placebo group remained on treatment (figure 1).

Baseline demographics and disease characteristics were well balanced between groups. In the overall population, the median age was 64 years; 63% of patients had a tumour with *RAS* mutation, and 72% of patients had liver metastases. The median number of prior therapies was 4 for metastatic disease; 73% of patients had received more than three prior lines of therapy for metastatic disease. Overall, 96% of patients had received prior anti-VEGF therapy and 39% had prior anti-EGFR therapy; all patients had prior treatment with either trifluridine/tipiracil (52%), regorafenib (8%), or both (39%) (table 1).

The median duration of exposure was 3·1 months (IQR, 1·8–5·6) (mean ±[standard deviation] SD, 4·0±3·1) for fruquintinib and 1·8 months (IQR, 1·0–2·3) (mean ±SD, 2·0±1·3) for placebo. Median number of treatment cycles was 3·0 (IQR, 2·0–6·0) for fruquintinib and 2·0 (IQR, 1·0–3·0) for placebo; 223 patients (49%) on fruquintinib received four or more treatment cycles versus 34 patients (15%) on placebo. The median relative dose intensity was 92% and 98%, respectively (appendix table 1, p 10). After ending study treatment, 134 patients (29%) on fruquintinib and 79 patients (34%) on placebo received additional treatment during survival follow-up (appendix table 2, p 11). There were 22 patients (3%) excluded from the per-protocol analysis population due to their potential impact on the efficacy evaluation; the excluded patients were balanced between groups, with 17 patients (4%) on fruquintinib and 5 patients (3%) on placebo (appendix table 3, p 16).

The primary analysis was performed after 490 (71%) deaths: 317 (69%) in the fruquintinib group and 173 (75%) in the placebo group. Loss to follow-up or withdrawal of consent was low in the study with 17 patients (4%) in the fruquintinib and 8 patients (3%) in the placebo group. Median follow-up was 11·3 months in the fruquintinib group and 11·2 months in the placebo group. The median overall survival was 7·4 months (95% CI 6·7–8·2) with fruquintinib and 4·8 months (95% CI 4·0–5·8) with placebo, for an absolute improvement in median overall survival of 2·6 months with fruquintinib and a 34% reduction in the risk of death with fruquintinib compared with placebo (stratified hazard ratio 0·66; 95% CI 0·55–0·80; p<0·001) (figure 2A).

The Kaplan–Meier plot (figure 2A) shows an early separation of the curves in favour of the fruquintinib group that is 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 have an impact on the validity and interpretability of the hazard ratio. The proportion of patients who were still alive at 9 months was 41% (95% CI 36·4–45·8) in the fruquintinib group and 28% (95% CI 22·1–34·3) in the placebo group.

A total of 605 patients (88%) 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) with fruquintinib and 1·8 months (95% CI 1·8–1·9) with placebo, for an absolute improvement in median progression-free survival of 1·9 months and a 68% reduction in the risk of disease progression or death with fruquintinib compared with placebo (stratified hazard ratio 0·32; 95% CI 0·27–0·39, p<0·001) (figure 2B). For progression-free survival, there was no violation of the proportional-hazard assumption.

Subgroup analyses of overall survival and progression-free survival were consistent with the benefit observed in the intention-to-treat population across essentially all prespecified subgroups, including randomisation stratification factors: prior therapy with trifluridine/tipiracil and/or regorafenib, *RAS* mutation status, and duration of metastatic disease (figures 3A and 3B).

Investigator-assessed objective response rate was documented in seven patients (2%) in the fruquintinib group compared with zero patients in the placebo group (95% CI 0·4–2·7; p=0·059). No complete responses were observed (table 2). The median duration of response for fruquintinib was 10·7 months (95% CI 3·9–not estimable); maximum duration of response is ongoing at 16·9+ months. The disease control rate was 56% for patients treated with fruquintinib compared with 16% for patients treated with placebo (95% CI 32·8–46·0; p<0·001).

Overall, 451 patients (99%) in the fruquintinib group and 213 patients (93%) in the placebo group experienced at least one adverse event. The most frequent any-grade events, regardless of causality, observed with fruquintinib versus placebo were hypertension (168 [37%] vs 20 [9%]) and asthenia (155 [34%] vs 52 [23%]). Grade 3 or higher adverse events occurred in 286 patients (63%) receiving fruquintinib compared with 116 patients (50%) receiving placebo; the most frequent of these events were hypertension (62 [14%] vs 2 [1%]), asthenia (35 [8%] vs 9 [4%]), and hand-foot syndrome (29 [6%] vs 0%). The incidence of serious adverse events was similar between groups. Adverse events led to death in 49 patients (11%) receiving fruquintinib

and 45 patients (20%) receiving placebo, with disease progression as the most frequently reported term in each group (31 [7%] and 30 [13%], respectively); one patient on placebo died from COVID-19. One death in each group was considered treatment related (intestinal perforation in the fruquintinib group, cardiac arrest in the placebo group) (table 3).

Dose interruptions due to adverse events occurred in 213 patients (47%) receiving fruquintinib and 61 patients (27%) receiving placebo. Dose reductions due to adverse events occurred in 110 patients (24%) on fruquintinib and nine patients (4%) on placebo (appendix table 4, p 16); 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 table 5, p 17). Overall, 93 patients (20%) on fruquintinib and 49 patients (21%) on placebo discontinued treatment due to adverse events; asthenia was the most frequent reason for fruquintinib discontinuation (7 patients, 2%) (appendix tables 4 and 6, pp 16-17).

Discussion

The multiregional, phase 3 FRESCO-2 study conducted in the United States, Europe, Japan, and Australia met its primary and key secondary endpoints, demonstrating statistically significant improvements in overall survival and progression-free survival 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 on fruquintinib versus 1% on placebo were progression free. The overall survival improvement seen with fruquintinib is further supported by the performance of the placebo group, which is comparable 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 treated with fruquintinib stayed on treatment almost twice as long as those on placebo (median, 3·1 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] While grade 3 or higher adverse events occurred in 63% versus 50% on placebo, 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 to 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%, respectively). The discontinuation rates observed here likely reflect the refractory patient population in this study.

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

Overall survival and progression-free survival benefits were also consistent regardless of number of prior 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 more than three prior lines for metastatic disease) as well as the efficacy of fruquintinib in earlier lines of therapy (27% had three or fewer prior lines for metastatic disease). Consistent with these latter results, the activity of fruquintinib has previously been shown in patients without extensive prior anti-VEGF, trifluridine/tipiracil, or regorafenib.[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 recently completed phase 3 SUNLIGHT trial evaluated the role of trifluridine/tipiracil with or without bevacizumab in patients following two prior lines of prior therapy in metastatic colorectal cancer; nearly 24% of the patients did not receive a prior anti-VEGF agent reflecting the earlier line of therapy in which it was conducted.[18] Patients in FRESCO-2 were required to have prior treatment with targeted therapies where approved and available in participating countries. Moreover, the majority of patients had received a prior anti-VEGF biologic agent as well as trifluridine/tipiracil and/or regorafenib. As a result, the primary results of FRESCO-2 demonstrate 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 refractory metastatic colorectal cancer[10,11,19,20] in multiple settings.

FRESCO-2 was conducted during the global COVID-19 pandemic during a time when institutional participation in clinical studies was limited. Nevertheless, enrollment was completed in less than 17 months, underscoring the high unmet need of this metastatic colorectal cancer patient population.

A limitation of this study is that the COVID-19 pandemic hindered the completion of blood-based ctDNA correlative analyses as unanticipated supply chain issues prevented the timely distribution and collection of test kits necessary to collect samples. While the inability to complete these exploratory analyses prevented a deeper understanding of patients who may 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. This statistically significant and clinically meaningful benefit was coupled with a favourable safety profile in heavily pretreated patients with refractory

metastatic colorectal cancer from a global population representing current treatment practices. Results from FRESCO-2 support fruquintinib as a new global oral treatment option and will add to the limited armamentarium for patients with refractory metastatic colorectal cancer, which will enrich the continuum of care for these patients.

Contributors

AD, JTa, TY, AS, EVC, JCY, CE conceptualised and designed the study. ZY, JJ, RGC, AD, JTa, TY, TS, ASh, SN, AS-B, ASo, LF, EVC, DA, FG, CE, PGA, SL, JTo ASP, AB contributed to the collection and assembly of the data. ZY, FG, JJ, RGC, AD, JTa, TY, TS, SN, ASo, EVC, DA, JY, MD, FG, CE, PGA, SL, 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 vouched for the accuracy and thoroughness of the data and for the fidelity of the study to the statistical analysis plan and study protocol.

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Data sharing

The study protocol and statistical anlaysis 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 William Schelman (williams@hutch-med.com) for consideration

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TABLES

Table 1: **Baseline demographic and disease characteristics (intention-to-treat population)**

Characteristic	Fruquintinib (N=461)	Placebo (N=230)
Age		
Median – year (IQR)	64 (56-70)	64 (56-69)
≥ 65 years	214 (46)	111 (48)
Sex		
Female	216 (47)	90 (39)
Male	245 (53)	140 (61)
Race		
White	367 (80)	192 (84)
Asian	43 (10)	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/unknown	36 (8)	14 (6)
Region		
North America	82 (18)	42 (18)
Europe	329 (71)	166 (72)
Japan	40 (9)	16 (7)
Australia	10 (22)	6 (3)
ECOG PS score*		
0	196 (43)	102 (44)
1	265 (58)	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 only	143 (31)	70 (30)
Liver metastases	339 (74)	156 (68)
Duration of metastatic disease†		
≤18 months	37 (8)	13 (6)
>18 months	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/unknown	53 (12)	22 (10)
Microsatellite/mismatch repair status		
MSS and/or pMMR	427 (93)	215 (94)
MSI-H and/or dMMR	5 (1)	4 (2)
Unknown	29 (6)	11 (5)
Number of prior treatment lines in metastatic disease		
Median – n (IQR)	4 (3-6)	4 (3-6)
Number of prior treatment lines in metastatic disease		
≤3	125 (27)	64 (28)
>3	336 (73)	166 (72)
Prior 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)
Prior trifluridine/tipiracil and/or regorafenib		
Trifluridine/tipiracil	240 (52)	121 (53)
Regorafenib	40 (9)	18 (8)
Both	181 (39)	91 (40)

Data are n (%) unless otherwise noted.

* Eastern Cooperative Oncology Group performance status (ECOG PS) 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.

dMMR=deficient mismatch repair. EGFR=epidermal growth factor receptor. MSI-H=microsatellite instability-high. MSS=microsatellite stable. pMMR=proficient mismatch repair. VEGF=vascular endothelial growth factor.

Table 2: **Summary of Efficacy Results (intention-to-treat population)**

	Fruquintinib (N=461)	Placebo (N=230)	Treatment effect	Two-sided p value
Time-to-event endpoints			Hazard ratio (95%CI)	
Overall survival				
Median – months (95% CI)	7·4 (6·7, 8·2)	4·8 (4·0, 5·8)	0·66 (0·55, 0·80)	<0.001
Progression-free survival				
Median – months (95% CI)	3·7 (3·5, 3·8)	1·8 (1·8, 1·9)	0·32 (0·27, 0·39)	<0.001
Antitumour activity endpoints			Adjusted difference (95%CI)	
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)		
Not applicable[†]	60 (13)	49 (21)		
Objective response				
Patients	7 (2)	0		
95% CI	(0·6, 3·1)	(0, 1·6)	2 (0·4, 2·7)	0·059
Disease control rate				
Patients	256 (56)	37 (16)		
95% CI	(50·9, 60·1)	(11·6, 21·5)	39[‡] (32·8, 46·0)	<0·001
Duration of response				
Median – months (range)	10·7 (2·1+, 16·9+)[§]	0		
95% CI	(3·9, NE)	NA		

Data are n (%) unless otherwise noted.

[*] The denominators for the percentages are patients in the intention-to-treat population, which included all patients who underwent randomisation. 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 includes patients for whom no baseline or postbaseline imaging were performed.

[‡] Percentage reflects adjusted difference prior to rounding in each group.

[§] The Kaplan–Meier method for censored data was used to calculate duration. A plus sign indicates no progressive disease or death by the time of the last assessment.

NA=not applicable. NE=not estimable.

Table 3: **Adverse events (safety population)[*]**

	Fruquintinib (N=456)		Placebo (N=230)	
	Any grade	**Grade ≥3**	**Any grade**	**Grade ≥3**
At least one adverse event	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 (4)	1 (<1)
Vomiting	66 (15)	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
AST increased	48 (11)	10 (2)	11 (5)	3 (1)
ALT increased	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
Any serious adverse event	172 (38)	163 (36)[†]	88 (38)	85 (37)[†]
Adverse events leading to death[‡]	49 (11)	49 (11)	45 (20)	45 (20)
Any adverse event of special interest	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)
Infections	96 (21)	30 (7)	29 (13)	13 (6)
Proteinuria	79 (17)	8 (2)	12 (5)	2 (1)
Haemorrhages	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 decreased	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 higher 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. ALT=alanine aminotransferase. AST=aspartate aminotransferase.

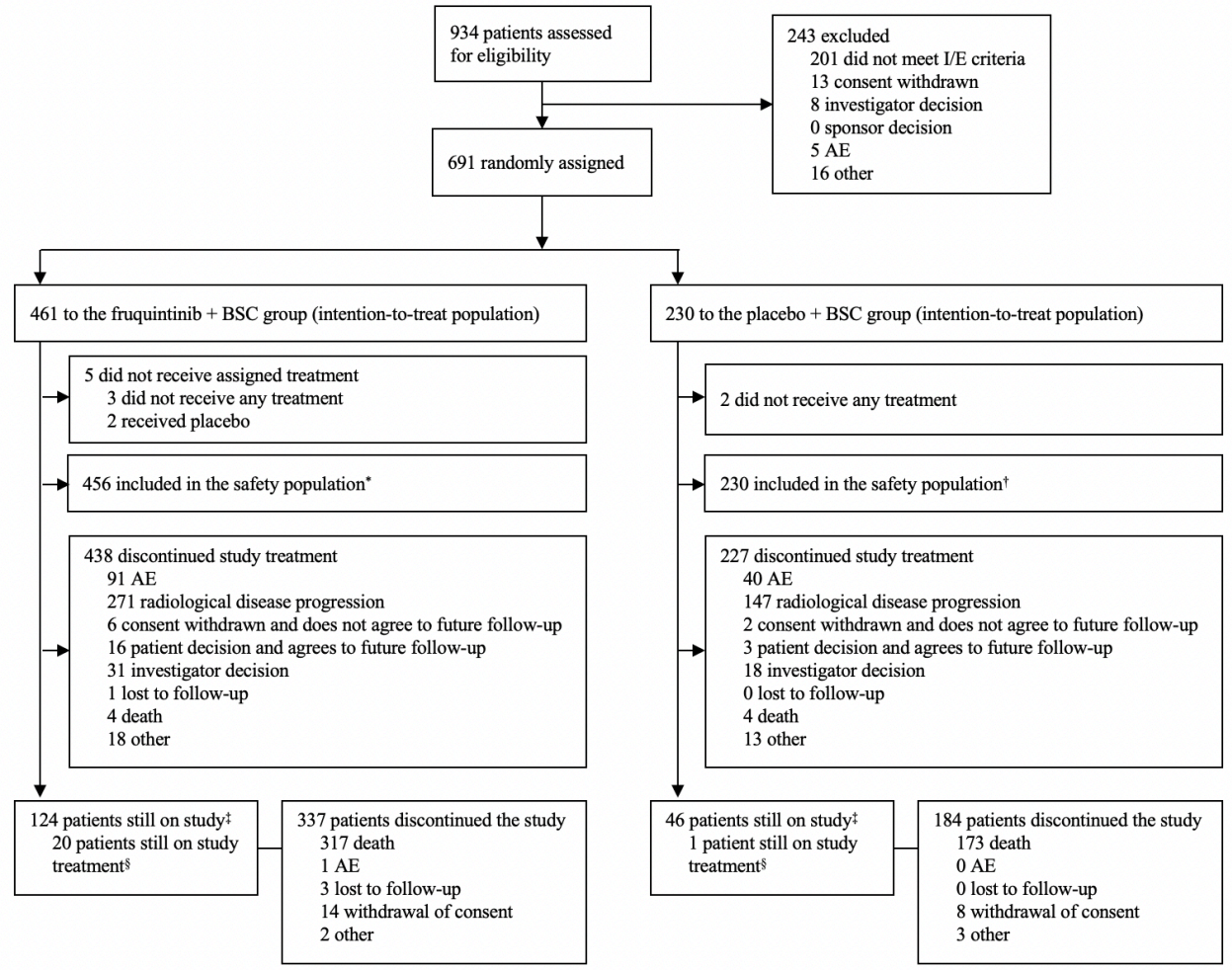
[†] Most frequent (≥2%) grade 3 or higher serious adverse events with fruquintinib compared with placebo were pneumonia (2% vs <1%) and abdominal pain (2% vs 1%).

[‡] 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 higher adverse events of special interest with fruquintinib compared with placebo were hypertension (14% vs 1%) and hand-foot syndrome (under dermatological toxicity; 6% vs 0%).

FIGURES

Figure 1: **Study profile**



* Patients who were assigned fruquintinib and received fruquintinib.

† Patients who received placebo.

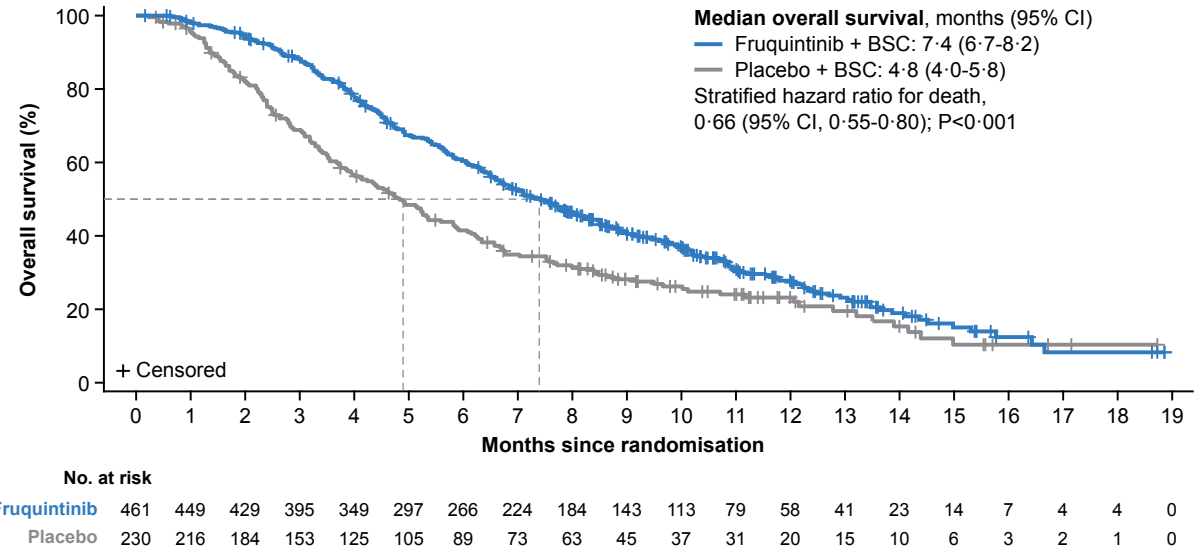
‡ Patients with missing end-of-study information were considered to be still on study.

§ Patients who received study drug but had missing end-of-treatment information were considered to be still on treatment.

AE=adverse event. BSC=best supportive care. I/E=inclusion/exclusion.

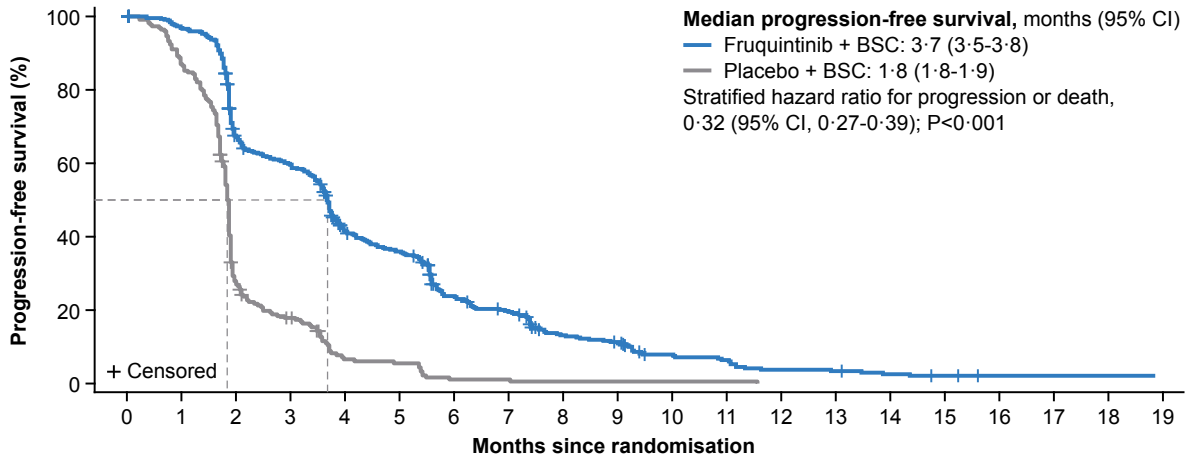
Figure 2: **Kaplan–Meier estimates of overall survival (A) and progression-free survival (B) in the intention-to-treat population** Tumour response was assessed locally according to RECIST v1·1 by investigators at screening and every 8 weeks (±1 week) thereafter. BSC=best supportive care.

A Overall survival



No. at risk																			
Fruquintinib	461	449	429	395	349	297	266	224	184	143	113	79	58	41	23	14	7	4	4	0
Placebo	230	216	184	153	125	105	89	73	63	45	37	31	20	15	10	6	3	2	1	0

B Progression-free survival

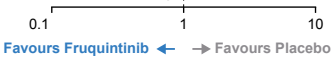


No. at risk																			
Fruquintinib	461	430	291	256	170	146	89	71	43	36	21	17	10	9	6	4	2	2	2
Placebo	230	194	60	36	12	10	2	2	1	1	1	1	0						

Figure 3: **Key subgroup analysis for overall survival (A) and progression-free survival (B) in the intention-to-treat population** Asia-Pacific includes Japan and Australia. ECOG PS=Eastern Cooperative Oncology Group performance score. EGFR=epidermal growth factor receptor. HR=hazard ratio. ITT=intention-to-treat. VEGF=vascular endothelial growth factor.

A Overall survival subgroup analysis

Subgroup		Fruquintinib no. deaths/ no. subjects	Placebo no. deaths/ no. subjects	Median months Fruquintinib	Median months Placebo	HR (95% CI)
ITT 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 PS	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	≤18 months	30/37	8/13	4·7	2·8	0·605 (0·260, 1·406)
	>18 months	287/424	165/217	7·6	4·9	0·642 (0·529, 0·779)
Primary tumour location at 1st 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)
Prior 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)
Prior 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)
Prior 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)
Prior trifluridine/tipiracil and/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)



B Progression-free survival subgroup analysis

Subgroup		Fruquintinib no. events/ no. subjects	Placebo no. events/ no. subjects	Median months Fruquintinib	Median months Placebo	HR (95% CI)
ITT 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 PS	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	≤18 months	35/37	11/13	1·9	1·8	0·361 (0·166, 0·787)
	>18 months	357/424	202/217	3·7	1·8	0·300 (0·249, 0·363)
Primary tumour location at 1st 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)
Prior 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)
Prior 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)
Prior 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)
Prior trifluridine/tipiracil and/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)