Real-World Data: Fruquintinib in Treating Metastatic Colorectal Cancer

Shuai Liu,*† Lu Lu,*† Feng Pan,‡ Chunsheng Yang,*† Jing Liang,§ Jinfeng Liu,¶ Jian Wang,# Rong Shen,** Fu-Ze Xin,†† and Nan Zhang*†

*Department of Breast Disease Diagnosis and Treatment Center, Central Hospital Affiliated to Shandong First Medical University, Jinan, P.R. China
†Department of Breast Disease Diagnosis and Treatment Center, Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan, P.R. China
‡Ethics Committee Office, Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, Jinan, P.R. China
§Department of Oncology, Shandong Provincial Qianfoshan Hospital, Jinan, P.R. China
¶Department of Oncology, Rizhao Hospital of Traditional Chinese Medicine, Rizhao, P.R. China
#Department of Medical Oncology, Qilu Hospital of Shandong University, Jinan, P.R. China
**Department of Chemotherapy, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, P.R. China
††Department of Gastrointestinal Surgery, Liao Cheng People’s Hospital, Liaocheng, P.R. China

Fruquintinib, also called HMPL-013, was first discovered by Hutchison Whampoa Pharmaceuticals Co. Ltd., Shanghai, China, and it is an oral vascular endothelial growth factor receptor (VEGFR) inhibitor. In clinical trials, fruquintinib has demonstrated a survival benefit in metastatic colorectal cancer (mCRC) patients. The purpose of this study was to retrospectively evaluate the efficacy and toxicity of fruquintinib in real-world patients. We collected data from patients with mCRC treated with oral fruquintinib from 2018 to 2020 in six different institutions. Patients with mCRC initially received 5 mg of oral fruquintinib daily for 3 weeks. Progression-free survival (PFS) was evaluated using the Kaplan–Meier method. The efficacy and safety of fruquintinib were also assessed. Seventy-five patients were involved in our study, and 29.3% of patients achieved stable disease (SD). Median PFS was 5.4 months (95% CI: 4.841–5.959). The treatment-emergent adverse events (TEAEs) with fruquintinib were acceptable with grade 3 TEAEs of 6%. The grade 3 TEAEs were hand–foot skin reaction (HFSR), fatigue, and stomatitis. ECOG performance status was associated with PFS. In this real-world study, the clinical activity of fruquintinib was consistent with what has been reported in previous clinical trials. The level of safety was acceptable, and the side effects were manageable.

Key words: Metastatic colorectal cancer (mCRC); Fruquintinib; Efficacy; Safety

INTRODUCTION

Globally, colorectal cancer (CRC) was the third leading cause of cancer deaths worldwide in 2020. Approximately 25% of CRC patients present with metastatic disease at the time of initial diagnosis, and 50% of CRC patients will eventually develop advanced, metastatic disease. Chemotherapy and targeted therapy are commonly used to treat unresectable metastatic CRC (mCRC). The conventional chemotherapy regimens for mCRC contain 5-fluorouracil (5-FU)/leucovorin with oxaliplatin or irinotecan. Antiangiogenic agents such as bevacizumab (Avastin; Genentech Inc., South San Francisco, CA, USA), ziv-aflibercept (Zaltrap; Regeneron, Tarrytown, NY, USA), and ramucirumab (Cyramza; Eli Lilly and Company, Indianapolis, IN, USA) are used in combination with chemotherapy. Epidermal growth factor receptor (EGFR)-targeted therapies (e.g., cetuximab and panitumumab) are effective in patients with wild-type KRAS. The vascular endothelial growth factor (VEGF) pathway is critical for the formation of new blood vessels and tumor pathogenesis. Vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR-TKI) is a small molecular antiangiogenic drug. Fruquintinib (also called HMPL-013 by Hutchison Whampoa Pharmaceuticals Co. Ltd.,

1These authors provided equal contribution to this work.
Address correspondence to Dr. Nan Zhang, Department of Breast Disease Diagnosis and Treatment Center, Central Hospital Affiliated to Shandong First Medical University, Jinan Central Hospital, Cheeloo College of Medicine, Shandong University, 105 Jiefang Road, Jinan, 250013 Shandong, P.R. China. Tel: +86 13370582850; E-mail: zlkzn2016@126.com
Shanghai, China) is a small-molecule inhibitor that targets the tyrosine kinase associated with VEGFR-1, VEGFR-2, and VEGFR-3, respectively, and has been used to treat mCRC. In phase II–III clinical trials, this agent has shown clinical activity with markedly improved overall survival (OS) with accepted safety and tolerability in mCRC patients. Depending on the results of the phase I–III trial, fruquintinib has been accepted as the first with mCRC patients. However, there are no related clinical studies investigating the efficacy and safety of fruquintinib in mCRC as third-line or later-line treatment in the real world.

We have conducted a retrospective study to analyze fruquintinib treatment in mCRC patients in real-world practice. This study was designed to measure the efficacy and toxicity of fruquintinib as a third-line or subsequent-line treatment in mCRC patients. The findings from our study will provide critical insights for the treatment of mCRC patients with fruquintinib in clinical practice.

MATERIALS AND METHODS

Patient Eligibility

The retrospective observational multicenter real-world analysis was conducted at the Jinan Central Hospital. The study protocol was approved by the independent ethics committee of each participating center. Eligible patients were between 18 and 80 years old. Informed consent for treatment was obtained from all patients. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was between 0 and 3. All mCRC patients underwent fruquintinib treatment as a third-line or greater treatment from December 2018 to November 2020. All mCRC patients involved in the investigation met histopathological criteria for CRC (World Health Organization, 2015), and advanced or recurrent stage IIIB/IV rectal colon cancer was verified by the TNM classification version 8. During fruquintinib therapy, patients did not receive any other treatments, including local modalities, such as interventional therapy or radiotherapy. Patients with recurrence or metastasis were verified based on the central radiologist’s interpretation by image scan [brain, chest, and abdominal computed tomography scans/magnetic resonance (MR), and/or bone scans].

Methods of Treatment

Baseline data, including patient demographics, laboratory data, ECOG PS, disease characteristics, treatment with systemic therapy, and toxicities with fruquintinib were recorded. Our aims were to identify the clinical characteristics of mCRC patients taking fruquintinib and to assess the efficacy and safety of fruquintinib in a real-world setting. At the discretion of the physicians, patients took 5 mg of fruquintinib for 3 weeks on and 1 week off. The dose of fruquintinib could be modified as per the product label and at the clinicians’ discretion. One dose reduction (5 to 4 mg; 4 to 3 mg) or withdrawal was performed for drug toxicity.

Safety and Adverse Reactions

The safety in our study was assessed by defining particularly unexpected, clinically significant adverse drug reactions (ADRs). Toxicity was graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events Version 4.03. Treatment-related adverse events were reported as explicitly stated in the file through the physicians or in the laboratory data gained during fruquintinib treatment.

Follow-Up

The primary clinical efficacy outcome of interest was progression-free survival (PFS). PFS was defined as the duration of time from the date of the first administration of fruquintinib to disease progression. Disease progression, stable disease, or partial response was defined radiographically, dependent on the radiologist’s final interpretation. Follow-up for patients was extended until November 1, 2020.

Statistical Analysis

Statistical analyses of our study were performed using SPSS software version 20.0 (SPSS Inc.; Selleck screening library Chicago, IL, USA). The p values were nominal and considered descriptive. Demographic characteristics of the patient population are summarized descriptively. Cox proportional hazards modeling was completed to evaluate predictors of outcomes. PFS was performed using the Kaplan–Meier method.

RESULTS

Patient Characteristics

We enrolled a total of 105 mCRC patients from January 2019 to November 2020 in our province. Thirty patients were excluded because case reports forms (CRFs) were not collected. We evaluated 75 mCRC patients for effectiveness and safety of fruquintinib treatment. Table 1 shows the baseline demographic and clinical characteristics of the mCRC patients. Fifty-six percent of patients were male, and 50.7% of patients were over the age of 60. A majority of patients (60%) had an ECOG PS of 0–1, and 40% had an ECOG PS ≥2. With respect to metastatic disease, 53.3% of patients had developed more than 1 metastatic site. The most common sites of metastasis were liver (65.3%), lung (46.7%), lymph nodes (30.6%), and bone (12%). Approximately 37% of patients had received three lines of systemic therapy, and 62.7% patients had received two lines of systemic therapy before fruquintinib treatment (Table 2). Most of these patients had previously been treated with bevacizumab (34.7%),
Furthermore, 12% of patients had been treated with immunotherapy, and 6.7% of patients had been previously treated with fruquintinib in combination with other agents. In addition, 25% of patients had been diagnosed with metastatic disease for more than 18 months before fruquintinib initiation.

### Table 1. Baseline Characteristics of Patients Treated With Fruquintinib

| Characteristic                              | N (%) |
|--------------------------------------------|-------|
| Patients                                   | 75 (100%) |
| Gender                                     |       |
| Male                                       | 42 (56.0%) |
| Female                                     | 33 (44.0%) |
| Age                                        |       |
| ≤60 years                                  | 37 (49.3%) |
| >60 years                                  | 38 (50.7%) |
| Performance status                         |       |
| 0                                          | 9 (12.0%) |
| 1                                          | 36 (48.0%) |
| 2                                          | 26 (34.7%) |
| 3                                          | 4 (5.3%) |
| Primary origin                             |       |
| Rectum                                     | 29 (38.7%) |
| Right hemicolon                            | 23 (30.7%) |
| Left hemicolon                             | 20 (26.7%) |
| Cecum                                      | 1 (1.3%) |
| Middle part of rectum and descending colon | 1 (1.3%) |
| Epityphlon                                  | 1 (1.3%) |
| Primary state                              |       |
| Not to remove                              | 9 (12.0%) |
| Has been removed                           | 66 (88.0%) |
| Metastatic sites                           |       |
| Liver                                      | 49 (65.3%) |
| Lung                                       | 35 (46.7%) |
| Bone                                       | 9 (12.0%) |
| Distant lymph node                         | 7 (9.3%) |
| Retroperitoneal lymph nodes                | 7 (9.3%) |
| Celiac lymph node                          | 6 (8.0%) |
| Pelvic cavity                              | 5 (6.7%) |
| Peritoneum                                 | 4 (5.3%) |
| Peri-intestinal lymph nodes                | 3 (4.0%) |
| Kidney                                     | 3 (4.0%) |
| Thyroid gland                              | 2 (2.7%) |
| Bladder                                    | 1 (1.3%) |
| Uterine adnexa                             | 1 (1.3%) |
| Adrenal gland                              | 1 (1.3%) |
| Brain                                      | 1 (1.3%) |
| Number of transferred organs               |       |
| >1                                         | 40 (53.3%) |
| 1                                          | 35 (46.7%) |
| Pleural effusion                           |       |
| No                                         | 71 (94.7%) |
| Yes                                        | 4 (5.3%) |
| Peritoneal effusion                        |       |
| No                                         | 60 (80.0%) |
| Yes                                        | 15 (20.0%) |
| Mismatched repair protein                  |       |
| pMMR/MSS                                   | 31 (41.3%) |
| dMMR/MSI-H                                 | 0 (0.0%) |
| Unknown                                    | 44 (58.7%) |

**Table 1. (Continued)**

| Characteristic                              | N (%) |
|--------------------------------------------|-------|
| Molecular pathology                        |       |
| RAS                                        |       |
| KRAS positive                              | 10 (13.3%) |
| NRAS positive                              | 3 (4.0%) |
| Negative                                   | 9 (12.0%) |
| Unknown                                    | 44 (58.7%) |
| BRAF                                       |       |
| Negative                                   | 4 (5.3%) |
| V600E positive                             | 0 (0.0%) |
| Unknown                                    | 71 (94.7%) |
| Time from diagnosis of metastatic disease  |       |
| ≤18 months                                 | 50 (66.7%) |
| >18 months                                 | 25 (33.3%) |

MMR, mismatch repair deficiency; MSI-H, microsatellite instability-high; MSS, microsatellite stabled; pMMR, mismatch repair proficient.

cetuximab (12%), and regorafenib (12%). Furthermore, 12% of patients had been treated with immunotherapy, and 6.7% of patients had been previously treated with fruquintinib in combination with other agents. In addition, 25% of patients had been diagnosed with metastatic disease for more than 18 months before fruquintinib initiation.

**Table 2. Characteristics of Fruquintinib Treatment in the Study Population**

| Characteristic                              | N (%) |
|--------------------------------------------|-------|
| Previous chemotherapy lines                |       |
| 2                                          | 47 (62.7%) |
| ≥3                                         | 28 (37.3%) |
| Prior targeted treatments                  |       |
| Bevacizumab                                 | 26 (34.7%) |
| Cetuximab                                  | 9 (12.0%) |
| Regorafenib                                | 14 (18.7%) |
| No                                         | 35 (46.7%) |
| Prior immunotherapy                        |       |
| No                                         | 66 (88.0%) |
| Yes                                        | 9 (12.0%) |
| Single or combined                         |       |
| Single                                     | 70 (93.3%) |
| Combined                                   | 5 (6.7%) |
| Dose reduction                             |       |
| Yes                                        | 2 (2.67%) |
| No                                         | 73 (97.3%) |
| Treatment interruption                     |       |
| Yes                                        | 0 (0.0%) |
| No                                         | 75 (100.0%) |
| Best response                              |       |
| Stable disease                             | 22 (29.3%) |
| Progressive disease                        | 45 (60.0%) |
| Death                                      | 8 (10.7%) |
Ninety-six percent of patients initiated fruquintinib treatment at the standard daily dose of 5 mg, while 4% of patients received the lower dose of 4 mg. In addition, 3% of patients needed dose reduction to 4 mg with no treatment interruption.

**Efficacy and Safety**

The assessments of the disease response rate to therapy included progressive disease in 60% patients, stable disease in 29.3% patients, and death in 10.7% patients (Table 2). All patients were evaluated for toxicity, and the treatment-emergent adverse events (TEAEs) that occurred with fruquintinib were recorded.

The most common grade 3 TEAEs were hand–foot skin reaction (HFSR), fatigue, and stomatitis. No grade 4 TEAEs were observed in any of the patients. No patients terminated the fruquintinib treatment, and two patients needed dose reductions (both 5 to 4 mg) for HFSR and fatigue. The grade 1–2 TEAEs are listed in Table 3.

The median PFS was 5.4 months [95% confidence interval (CI): 4.841–5.959]. Figure 1 shows the Kaplan–Meier survival curves for PFS in patients taking fruquintinib. Univariate analysis was also performed to analyze whether certain clinical features influenced PFS. Poor ECOG PS [\( \geq 2/0–1 \), hazard ratio (HR) = 0.477, 95% CI: 0.271–0.838, \( p = 0.010 \)] was associated with shorter PFS. We did not identify any other clinical features influencing PFS (Table 4).

**DISCUSSION**

To our knowledge, this is the first retrospective study to analyze the safety and efficacy of fruquintinib.

### Table 3. The Treatment Emergent Adverse Events (TEAEs) With Fruquintinib

| Adverse Events                  | Any Grade [n (%)] | Grade ≥3 [n (%)] |
|--------------------------------|-------------------|------------------|
| Any adverse event              | 37 (49.3%)        | 6 (8.0%)         |
| Hypertension                   | 14 (18.7%)        | 0                |
| Hand–foot skin reaction        | 12 (16.0%)        | 4 (5.3%)         |
| Fatigue                        | 9 (12.0%)         | 1 (1.3%)         |
| Diarrhea                       | 5 (6.7%)          | 0                |
| Anorexia                       | 5 (6.7%)          | 0                |
| Proteinuria                    | 4 (5.3%)          | 0                |
| Dysphonia                      | 4 (5.3%)          | 0                |
| Stomatitis                     | 4 (5.3%)          | 1 (1.3%)         |
| Muscle pain                    | 3 (4.0%)          | 0                |
| Emesis                         | 2 (2.7%)          | 0                |
| AST increased                  | 1 (1.3%)          | 0                |
| ALT increased                  | 1 (1.3%)          | 0                |
| Hypothyroidism                 | 1 (1.3%)          | 0                |
| Occult blood positive          | 1 (1.3%)          | 0                |
| Epistaxis                      | 1 (1.3%)          | 0                |
| Arthrodynia                    | 1 (1.3%)          | 0                |
| Dyspnea                        | 1 (1.3%)          | 0                |
| Abdominal distention           | 1 (1.3%)          | 0                |
| Hyperbilirubinemia             | 0                 | 0                |
| Thrombocytopenia               | 0                 | 0                |
| Weight loss                    | 0                 | 0                |

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

**Fruquintinib Treatment**

Ninety-six percent of patients initiated fruquintinib treatment at the standard daily dose of 5 mg, while 4% of patients received the lower dose of 4 mg. In addition, 3% of patients needed dose reduction to 4 mg with no treatment interruption.

Figure 1. Kaplan–Meier estimates of progression-free survival. (A) A total of 75 patients received fruquintinib treatment. The median progression-free survival (PFS) of the patients was 5.4 months [95% confidence interval (CI): 4.841–5.959]. (B) The PFS was significantly influenced by Eastern Cooperative Oncology Group (ECOG) performance status (PS) [\( \geq 2/0–1 \), hazard ratio (HR) = 0.477, 95% confidence interval (CI): 0.271–0.838, \( p = 0.010 \)].
FRUQUINTINIB IN METASTATIC COLORECTAL CANCER 29

treatment for mCRC patients in China in a real-world setting. Our findings show that fruquintinib has clinical efficacy against mCRC in later-line treatment and that the side effect profile was generally considered acceptable. It is estimated that there will be an estimated 376,000 new cases of CRC in China diagnosed each year, and the rate continues to increase. One half of cases will ultimately develop into advanced/metastatic disease6,7. With the improvement of targeted therapies, the treatment of mCRC has made outstanding progress.

It is now well established that the process of angiogenesis plays a critical role in tumor growth through the supply of key nutrients and oxygen. In addition, the formation of new blood vessels provides a convenient route for metastatic spread8. The VEGF/VEGFR system is the most important pathway leading to angiogenesis, which can stimulate endothelial cell proliferation, thereby promoting new vessel tube formation and migration9. In tumor tissue, tumor cells can produce VEGF by oncogenic activation or through loss of tumor suppressor function10,11 and by hypoxia condition or changing glucose concentrations12. The expression of VEGF-A by tumor cells is associated with poor prognosis in various tumor types, such as colon, gastric, lung, and melanoma13-16. The VEGF/VEGFR signal axis is an important target for cancer therapy17.

There are two major approaches that have been developed to target the VEGF/VEGFR signal pathway. One is VEGF or VEGFR neutralizing monoclonal antibodies, while the second approach is small-molecule inhibitors of VEGFR tyrosine kinase activity. The successful example is the anti-VEGF-A antibody bevacizumab (Avastin; Genentech Inc.), which has been approved for advanced mCRC in the first- and second-line setting combined with chemotherapy18. However, there are problems in the use of bevacizumab including immunogenicity and intravenous administration among others. There are several VEGFR small-molecule inhibitors, including regorafenib (Stivarga; BAY 73-4506; Bayer Healthcare Pharmaceuticals Inc., Wayne, NJ, USA)19, sunitinib (Sutent; Pfizer, New York, NY, USA)20, sorafenib (Nexavar; BayerHealthCare, Montville, NJ, USA; Onyx Pharmaceuticals, Emeryville, CA, USA)21, and pazopanib (Votrient; GlaxoSmithKline, Middlesex, England)22. Unfortunately, these agents have relatively low selectivity, as they can inhibit more than 10 kinases. As a result, they have significant off-target effects and are associated with significant side effects and limited anticancer efficacy. Fruquintinib is a highly selective angiogenesis inhibitor and was developed by Hutchison MediPharma for the treatment of solid tumors23. In 2018, fruquintinib received its first approval by the China Food and Drug Administration (CFDA) for the treatment of mCRC patients after two prior systemic therapies. Fruquintinib selectively targets the tyrosine kinases associated with VEGFR-1, VEGFR-2, and VEGFR-3, and it has demonstrated clinical activity and good tolerance levels23. In the phase Ib trial (NCT01975077), fruquintinib showed excellent pharmacokinetic characteristics, tolerable safety, and antitumor activity in various tumor types24. The median PFS was 5.8 months, and the median OS was 8.88 months. In the phase II trial (NCT02196688), fruquintinib treatment in mCRC was associated with a PFS of 4.73 months and a median OS of 7.72 months25. In the phase III clinical trial (NCT02314819), patients receiving fruquintinib treatment significantly improved PFS and OS in advanced mCRC1. The median OS in the fruquintinib treatment group was 9.3 months, and the median PFS in fruquintinib was 3.7 months. In this real-world study, the median PFS was similar to what was previously reported in the phase II trial (NCT02196688)25 and longer than that described in the phase III trial (NCT02314819)25. This difference may be attributed to the more rigorous enrollment eligibility criteria used in the clinical trials.

| Table 4 Factors Associated With Survival in Multivariate Analysis |
|------------------|------------------|------------------|
| Factor                        | HR (95%CI)       | p Value          |
| Age: ≤60/>60               | 0.835 (0.486–1.436) | 0.515 |
| Gender: male/female        | 1.208 (0.701–2.084) | 0.496 |
| ECOG: ≥2/0–1               | 0.477 (0.271–0.838) | 0.010 |
| Primary state: has been removed/not to remove | 1.110 (0.499–2.470) | 0.799 |
| Number of transferred organs: 1/>1 | 0.748 (0.432–1.294) | 0.300 |
| Pleural effusion: yes/no    | 0.549 (0.169–1.783) | 0.318 |
| Peritoneal effusion: yes/no | 0.731 (0.379–1.410) | 0.350 |
| Previous chemotherapy lines: 2/≥3 | 0.609 (0.350–1.060) | 0.079 |
| Prior targeted treatments: yes/no | 0.708 (0.410–1.223) | 0.215 |
| Prior immunotherapy: yes/no | 1.074 (0.481–2.396) | 0.861 |
| Single or combined therapy  | 1.360 (0.487–3.800) | 0.557 |
| Time from diagnosis of metastatic disease: ≤18 months/>18 months | 1.779 (0.930–3.404) | 0.082 |

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
Another reason for the difference in results may be due to the difference in baseline characteristics. As patients returned after a short follow-up period, we could not collect enough “outcomes” for OS. PS is known as a strong prognostic factor in patients with mCRC. Worsening PS has been associated with poor prognosis, which we have confirmed in our study. In the present study, PS was identified as the main independent factor for PFS. Patients with poor PS had shorter PFS. We were unable to identify any other predictive and/or prognostic factors for PFS. However, one word of caution as one limitation of our study is the relatively small sample size.

TEAEs associated with fruquintinib treatment were demonstrated in the phase Ib trial. The most common grade 3–4 TEAEs (incidence >5%) observed in 8% of patients were hypertension, HFSR, fatigue, and diarrhea. In the phase II trial, the grade 3–4 TEAEs (incidence >5%) observed in 61.7% of the fruquintinib treatment group were hypertension and HFSR. Dose reduction or treatment interruption for TEAEs occurred in 61.7% of patients treated with fruquintinib, and HFSR and hypertension were the most common TEAEs in the fruquintinib treatment group. In the phase III trial, the safety of fruquintinib treatment in cancer patients was further studied. The most common TEAEs were hypertension, HFSR, proteinuria, and dysphonia. Grade 3–4 TEAEs were observed in 46% of patients who received fruquintinib treatment. The most common grade 3–4 TEAEs (incidence >5%) were hypertension and HFSR.

Most of patients in our real-world study did not require treatment interruption or dose reduction. Three mCRC patients started with an oral dose of 4 mg given their baseline characteristic of having only a single kidney and advanced age. Two patients needed dose reduction to 4 mg because of HFSR and fatigue. Compared to the FRESCO trial, where 131 patients (47.1%) required interruption or dose reduction with fruquintinib treatment, a significantly smaller number of patients in our study required dose reduction. It seems that compared to the FRESCO trial, patients in our study tolerated fruquintinib well in the primary doses. This result might be due to the fact that follow-up time in our study was short. Therefore, a longer follow-up period in patients with fruquintinib treatment should be done in future analyses.

The disease control rate (stable disease or partial response) in our study was 29.3%, which is lower than 76.2% in the phase Ib trial, 68.1% in the phase II trial, and 62.2% in the FRESCO trial. The reasons for this discrepancy are still unclear. This finding may be the result of different baseline factors in our study. Furthermore, compared to the RRESSC trial population, fewer patients in our current study had been treated with immunotherapy, and some patients had received three lines of systemic therapy before the initiation of fruquintinib.

Another potential reason is that a small proportion of the patients in our study began their treatment with a reduced fruquintinib dose. Although the fruquintinib dose adjustment in patients was made following the doctor’s advice in our study, there was the possibility of noncompliance because patients self-administered the medication at home. One limitation of our current study is that it represents only a small sample size of patients with mCRC. All included patients who received fruquintinib were those deemed appropriate for treatment, which might not be possible for all patients with mCRC. We will continue our efforts to expand our studies with more mCRC patients who received fruquintinib treatment in the future.

CONCLUSIONS

Antiangiogenic therapy is an important strategy for mCRC treatment. Fruquintinib is a novel and highly selective treatment that targets VEGFR-1, VEGFR-2, and VEGFR-3 for cancer patients, and it plays a critical role in third-line mCRC treatment. Based on results shown in our current study, fruquintinib treatment in mCRC patients has an acceptable safety level. In real-world situations, fruquintinib treatment is associated with survival durations in cancer patients similar to those reported in randomized controlled trials. Furthermore, fruquintinib treatment showed controllable toxicity. Our future studies should use an enlarged sample size from multicenter studies of fruquintinib treatment and concentrate on the identification of patients who benefit from fruquintinib and minimizing toxicity.

ACKNOWLEDGMENTS: This work was supported by Shandong Medical and Health Science and Technology Development Project (grant No. 2016WS0136), Jinan Medical and Health Science and Technology Development Project (grant No. 2020-4-24), the Youth Fund from Natural Science Foundation of Shandong Province (grant No. ZR2020QH232), and Shandong First Medical University Academic Promotion Plan (grant No. 2019QLJD25). The authors declare no conflicts of interest.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 68(6):394–424.
2. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, Group EGW. 2014. Metastatic colorectal cancer: ESPMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 25(Suppl 3):iii1–9.
3. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D, Aranda Aguilar E, Bardelli A, Benson A, Bodoky G, Ciardiello F, D’Hoore A, Diaz-Rubio E, Douillard JY, Ducrœux M, Falcone A, Grothey A, Gruenberger T, Haustermans K, Heinemann V, Hof F, Kohne CH, Labianca R, Laurent-Puig P, Ma B, Maughan T, Muro K, Normanno N, Osterlund P, Oyen WJ, Papamichael D, Penheroudakis G, Pfeiffer P, Price TJ, Punt C, Ricke J, Roth A, Salazar R, Scheithauer W, Schmiol HJ, Tabernero J, Taieb J, Tejpar S, Wasan H, Yoshino T, Zaanan A, Arnold
D. 2016. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 27(8):1386–1422.

4. National Comprehensive Cancer Network (2020) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer. Version 4. 2020.

5. Li J, Qin S, Xu RH, Shen L, Xu J, Bai Y, Yang L, Deng Y, Chen ZD, Zhong H, Pan H, Guo W, Shu Y, Yuan Y, Zhou J, Xu N, Liu T, Ma D, Wu C, Cheng Y, Chen D, Li W, Sun S, Yu Z, Cao P, Chen H, Wang J, Wang S, Wang H, Fan S, Hua Y, Su W. 2018. Effect of fruquintinib vs placebo on overall survival in patients with previously treated metastatic colorectal cancer: The FRESCO randomized clinical trial. JAMA 319(24):2486–2496.

6. Chen W. 2015. Cancer statistics: Updated cancer burden in China. Chin J Cancer Res. 27(1):1.

7. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu QX, He J. 2016. Cancer statistics in China, 2015. CA Cancer J Clin. 66(2):115–132.

8. Kerbel RS. 2008. Tumor angiogenesis. N Engl J Med. 359(19):2039–2049.

9. Dvorak HF. 2002. Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumour angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol. 20(21):4368–4380.

10. Rak J, Mitsushashi Y, Bayko L, Filmus J, Shirasawa S, Sasazuki T, Kerbel RS. 1995. Mutant ras oncogenes upregulate VEGF/VPF expression: Implications for induction and inhibition of tumour angiogenesis. Cancer Res. 55(20):4575–4580.

11. Farhang Ghahremani M, Goossens N, Nittner D, Bisteau X, Bartunkova S, Zvolinska A, Hulpiau P, Haigh K, Haenebalcke L, Drogat B, Jochemsen A, Roger PP, Marine JC, Haigh JJ. 2013. p53 promotes VEGF expression and angiogenesis in the absence of an intact p21-Rb pathway. Cell Death Differ. 20(7):888–897.

12. Raja R, Kale S, Thorat D, Soundararajan G, Lohite K, Mane A, Karnik S, Kundu GC. 2014. Hypoxia-driven osteopontin contributes to breast tumor growth through modulation of HIF1alpha-mediated VEGF-dependent angiogenesis. Oncogene 33(16):2053–2064.

13. Martins SF, Garcia EA, Luz MA, Pardal F, Rodrigues M, Filho AL. 2013. Clinicopathological correlation and prognostic significance of VEGF-A, VEGF-C, VEGFR-2 and VEGFR-3 expression in colorectal cancer. Cancer Genomics Proteomics 10(2):55–67.

14. Wang X, Chen X, Fang J, Yang C. 2013. Overexpression of both VEGF-A and VEGF-C in gastric cancer correlates with prognosis, and silencing of both is effective to inhibit cancer growth. Int J Clin Exp Pathol. 6(4):586–597.

15. Chatterjee S, Heukamp LC, Siobal M, Schottle J, Wieczorek C, Peifer M, Frasca D, Koker M, Konig K, Meder L, Rauh D, Buettner R, Wolf J, Brekken RA, Neumaier B, Christofori G, Thomas RK, Ullrich RT. 2013. Tumor VEGF:VEGFR2 autocrine feed-forward loop triggers angiogenesis in lung cancer. J Clin Invest. 123(4):1732–1740.

16. Simonetti O, Lucarini G, Rubini C, Goteri G, Zizzi A, Staibano S, Campanati A, Gangetti G, Di Primio R, Offidani A. 2013. Microvessel density and VEGF, HIF-1alpha expression in primary oral melanoma: correlation with prognosis. Oral Dis. 19(6):620–627.

17. Scott AM, Allison JP, Wolchok JD. 2012. Monoclonal antibodies in cancer therapy. Cancer Immun. 12:14.

18. Mochler M, Sprinzl MF, Abdelfattah M, Schimanski CC, Adami B, Godderz W, Majer K, Flieger D, Teufel A, Siebler J, Hoehler T, Galle PR, Kanzler S. 2009. Capcetibine and irinotecan with and without bevacizumab for advanced colorectal cancer patients. World J Gastroenterol. 15(4):449–456.

19. Sartore-Bianchi A, Zeppellini A, Amatu A, Ricotta R, Bencardino K, Siena S. 2014. Regorafenib in metastatic colorectal cancer. Expert Rev Anticancer Ther. 14(3):255–265.

20. Grandinetti CA, Goldspiel BR. 2007. Sorafenib and sunitinib: Novel targeted therapies for renal cell cancer. Pharmacotherapy 27(8):1125–1144.

21. Keating GM, Santoro A. 2009. Sorafenib: A review of its use in advanced hepatocellular carcinoma. Drugs 69(2):223–240.

22. van Geel RM, Beijnen JH, Schellens JH. 2012. Concise drug review: Pazopanib and axitinib. Oncologist 17(8):1081–1089.

23. Sun Q, Zhou J, Zhang Z, Guo M, Liang J, Zhou F, Long J, Zhang W, Yin F, Cai H, Yang H, Zhang W, Gu Y, Ni L, Sai Y, Cui Y, Zhang M, Hong M, Sun J, Yang Z, Qing W, Su W, Ren Y. 2014. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. Cancer Biol Ther. 15(12):1635–1645.

24. Cao J, Zhang J, Peng W, Chen Z, Fan S, Su W, Li K, Li J. 2016. A phase 1 study of safety and pharmacokinetics of fruquintinib, a novel selective inhibitor of vascular endothelial growth factor receptor-1, -2, and -3 tyrosine kinases in Chinese patients with advanced solid tumors. Cancer Chemother Pharmacol. 78(2):259–269.

25. Xu RH, Li J, Bai Y, Xu J, Liu T, Shen L, Wang L, Pan H, Cao J, Zhang D, Fan S, Hua Y, Su W. 2017. Safety and efficacy of fruquintinib in patients with previously treated metastatic colorectal cancer: A phase Ib study and a randomized double-blind phase II study. J Hematol Oncol. 10(1):22.

26. Sorbye H, Kohne CH, Sargent DJ, Glimelius B. 2007. Patient characteristics and stratification in medical treatment studies for metastatic colorectal cancer: A proposal for standardization of patient characteristic reporting and stratification. Ann Oncol. 18(10):1666–1672.

27. Stillwell AP, Ho YH, Veitch C. 2011. Systematic review of prognostic factors related to overall survival in patients with stage IV colorectal cancer and unresectable metastases. World J Surg. 35(3):684–692.

28. Massacesi C, Norman A, Price T, Hill M, Ross P, Cunningham D. 2000. A clinical nomogram for predicting long-term survival in advanced colorectal cancer. Eur J Cancer 36(16):2044–2052.