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Fruquintinib: A new arrow in the quiver for metastatic colorectal cancer care

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Abstract

One of the main causes of the worldwide cancer burden is Colorectal Cancer (CRC), and thanks to the development of new drugs and the growing number of patients receiving local treatments and the best supportive care, considerable advancements have been made in survival. However, the prognosis for patients resistant to fluoropyrimidines, irinotecan, oxaliplatin and target therapies is dismal, highlighting the urgent need for the research and application of new treatment options. Vascular Endothelial Growth Factor (VEGF) was isolated and cloned for the first time in 1989 by Ferrara and Henzel at Genentech. Their finding opened the door to a more thorough comprehension of neo angiogenesis function in cancer. Bevacizumab, aflibercept, ramucirumab, and regorafenib are among the anti-angiogenic drugs that have been licensed for mCRC in recent decades. The most recent addition to this arsenal is fruquintinib, also known as HMPL-013, an oral tyrosine kinase inhibitor of VEGF receptor (VEGFR)-1, VEGFR-2, and VEGFR-3 that is very selective.

Keywords: Colorectal neoplasm; Fruquintinib; Neoangiogenesis; Vascular endotelial growth factor; Fluoropyrimidines.

Introduction

Due to the development of research on news drug and the growing number of patients receiving local treatments, the prognosis for patients with Metastatic Colorectal Cancer (mCRC) has been improving steadily [1].

Angiogenesis plays a crucial role in this disease, and since the discovery of Vascular Endothelial Growth Factor (VEGF), a lot of therapies that target this pathway have been developed [2,3].

The Tyrosine Kinase Inhibitor (TKI) fruquintinib (HMPL-013) mainly inhibits the Vascular Endothelial Growth Factor Receptor (VEGFR), with a small amount of activity in other targets like CD117 (cluster of differentiation 117, or KIT), Fibroblast Growth Factor Receptor 1 (FGFR1), and Platelet-Derived Growth Factor Receptor (PDGFR) [4]. Hutchison MediPharma (Shanghai, China) developed the first research on this drug, and in 2013, Eli Lilly (Indianapolis, IN, USA) co-developed and marketed it [5].

Based on the results of the phase III FRESCO trial, which compared the efficacy and safety of fruquintinib versus Best Support Care (BSC) in patients with advanced colorectal cancer who had failed at least two lines of chemotherapy, the Chinese National Medical Products Administration, approved the drug in 2018 for the treatment of patients with mCRC [6].

More recently, the FRESCO-2 trial (a global multicenter randomised placebo-controlled phase 3 trial to compare the efficacy and safety of fruquintinib plus best supportive care to placebo plus best supportive care in patients with refractory mCRC; ClinicalTrials.gov identifier: NCT04322539) showed that fruquintinib was more effective than placebo in patients with mCRC who had previously received treatment with all of the conventional protocols, such as regorafenib and/or trifluridine/tipiracil (FTD/TPI, TAS-102) [7].

The new drug use for fruquintinib in mCRC has been given priority assessment by the US Food and Drug Administration (FDA) [8].

This review will provide a summary of development of study for fruquintinib and highlight potential opportunities for further investigation.

Preclinical evaluations

With a half-maximal Inhibitory Concentration (IC50) at a low nanomolar level, fruquintinib inhibited VEGFR family kinases and decreased Vascular Endothelial Growth Factor (VEGF)/VEGFR cell signalling in human umbilical vein endothelial cells and human lymphatic endothelial cells in vitro. VEGFR-1, VEGFR-2, and VEGFR-3 are the targets of this small molecules VEGFR inhibitor with great kinome selectivity, while c-kit, PDGFR, Rearranged During Transfection (RET), and FGFR-1 are very weakly inhibited.

Meanwhile, angiogenesis suppresses the immune system by a variety of methods, such as directly inhibiting immunological effector cells and antigen-presenting cells. Myeloid-Derived Suppressor Cells (MDSCs), tumor-associated macrophages, and regulatory T cells (Treg) are also upregulated in this process. Fuquintinib is one example of an anti-angiogenic drug that has become a viable alternative for modifying the Tumour Microenvironment (TME) [9].

Many xenograft models were used to assess anti-tumor effect in vivo, and studies of plasma concentration have confirmed the link between drug exposure and anti-tumor activity [10].

To achieve >80% tumour growth inhibition, Sun et al. demonstrated preclinical activity using several mouse models of different tumours. Such as results from the gastric cancer model (BGC-823) showed that the drug concentration must be kept at least above the drug concentration needed to inhibit the receptor phosphorylation by 85% (EC85) for about 8 hours [10].

Moreover, the molecule showed good pharmacokinetic characteristics, such as quick absorption, high oral bioavailability, slow excretion, appropriate tissue distribution, and a low likelihood of drug-drug interactions [4].

Additionally, in many patient-derived xenograft models, fruquintinib has shown improved anti-tumor effectiveness when paired with cytotoxic treatment with a respectable tolerance [10].

Finally, fruquintinib has shown a synergistic effect with FTD/TPI in nude mouse models employing two human Colorectal Cancer (CRC) xenografts (SW48 and HCT 116) [11].

To treat solid tumours, a variety of TKIs have been developed. The wider range of kinase inhibition, however, limits their effectiveness at the Maximum Tolerated Dosage (MTD) and may result in increased toxicity and/or less than ideal inhibition of a particular target. For instance, fruquintinib demonstrated a greater selectivity to VEGFR in comparison to regorafenib [5,12]

A panel of 253 kinase tests showed that only a small number of kinases other than VEGFRs were inhibited, which may reduce off-target toxicity and permit a larger dose at MTD [5,12].

Fruquintinib and clinical trials in metastatic colorectal cancer

Initial study about fruquintinib in refractory mCRC showed tolerable toxicity and moderate efficacy, as previously established in pivotal trials with regorafenib and FTD/TPI. This led to the start a pivotal phase III trial (FRESCO) (Table 1) [5-7,13,14].

Table 1: Clinical studies with fruquintinib in metastatic colorectal cancer.

Clinical trial identifier	Phase	Line	N	mOS with fruquintinib (months)	mOS with control (months)	mPFS with fruquintinib (months)	mPFS with control (months)	ORR with fruquintinib (%)	ORR with control (%)
NCT01975077 [5]	Ib	Third	42	8.88	NA	5.8	NA	9.5	NA
NCT02196688 [13]	II	Third	71	7.72	5.52	4.73	0.99	2.1	0
NCT02314819 (FRESCO) [6]	III	Third	416	9.3	6.6	3.7	1.8	4.7	0
NCT04322539 (FRESCO-2) [7]	III	Later	691	7.4	4.8	3.7	1.8	1.5	0

mOS: Median Overall Survival; mPFS: Median Progression-Free Survival; ORR: Objective Response Rate; NA: Not Applicable.

The phase I clinical trials pharmacokinetic data supported the idea of a once-daily taking by confirming that plasma exposure at MTD could produce an EC85 for 24 hours [12].

FRESCO trial, phase III

FRESCO was a multicenter, phase III clinical trial that involved 416 patients in 28 Chinese institutions and was double-blind, placebo-controlled, and randomised [6]. The trial involved a 2:1 randomisation of patients who had undergone at least two lines of chemotherapy to either fruquintinib (5 mg orally once daily, 3 weeks on, followed by 1 week off) or a placebo.

With a median overall survival (mOS) of 9.30 months (95% CI 8.18–10.45) with fruquintinib and 6.57 months (95% CI 5.88–8.11) with a placebo, the FRESCO trial achieved its primary end point (Hazard Ratio [HR] for death 0.65 [95% CI 0.51–0.83]; p<0.001). The Median Progression-Free Survival (mPFS), the secondary end point, was similarly significantly higher with fruquintinib (3.71 months [95% CI 3.65–4.63] compared to 1.84 months [95% CI 1.81–1.84] in the placebo arm; HR 0.26 [95% CI 0.21–0.34]; p<0.001). The objective response rate with fruquintinib was low, as was previously shown with other treatments in subsequent lines: 4.7% versus 0% (p=0.01). With fruquintinib, the Disease Control Rate (DCR) was 62.2%, while with a placebo, it was 12.3% (p<0.001).

Regarding toxicity, 21.2% had grade 3–4 hypertension, 10.8% had Hand–Foot Syndrome (HFS), and 3.2% had proteinuria. Furthermore, 47.1% of patients treated with fruquintinib experienced a treatment interruption or dose decrease because of these toxicities, compared to 13.1% of patients treated with a placebo. Among these, thrombocytopenia (5.4%), proteinuria (9.7%), and HFS (13.3%) were the most frequent reasons for stopping or reducing the dosage.

FRESCO-2 phase III study; Fruquintinib in metastatic colorectal cancer

Another key study was the FRESCO-2 trial, which recruited patients with mCRC who was previously treated with chemotherapy consisting fluoropyrimidine, oxaliplatin, or irinotecan, a

VEGF inhibitor and, if they had a Rat Sarcoma virus gene (RAS) wild-type, an epithelial growth factor receptor inhibitor [7].

Furthermore, patients had to be in progression or intolerant to Regorafenib and FTD/TPI (TAS 102) [6,7] highlights the variations in the study population and eligibility requirements between the two-phase III trials.

The primary endpoint, OS, was meet with mOS in fruquintinib arm of 7.4 months (95% CI 6.7–8.2), while the placebo arm of 4.8 months (95% CI 4.0–5.8) (HR 0.66 [95% CI 0.55–0.80]; p<0.0001).

A clear drawback of each one trial was the lack of a biomarker predictor of response, which makes decision-making even more challenging in situations where there are at least two alternative possibilities.

Once more, 98.9% of patients receiving fruquintinib suffered Treatment-Emergent Adverse Effects (TEAEs) of any grade, compared to 92.6% of patients receiving placebo. Of these, 62.7 and 50.4% of patients experienced grade 3 or severe toxicities. In the fruquintinib and placebo arms, the most common grade 3 or worse TEAEs were fatigue (3.9 versus 0.9%), asthenia (7.7 versus 3.9%), decreased appetite (2.4 versus 1.3%), diarrhoea (3.5 versus 0%), hypothyroidism (0.4 versus 0), and HFS (6.4 versus 0%). Additionally, fruquintinib treatment resulted in dose reductions in 24% of patients and interruptions in 47% of patients. This is encouraging, especially given the later-line situation of these patients, and compares favourably with regorafenib. Similar percentages of patients (20 in the fruquintinib group and 21% in the placebo group) stopped taking the medication because of side effects [7].

Current research in colorectal cancer

By causing vascular normalisation and immunological reprogramming, inhibiting neoangiogenesis oppose the immunosuppressive environment of the TME and makes fruquintinib an option for synergistic use with Immune Checkpoint Inhibitors (ICIs). Given its selectivity, fruquintinib may be a better ICI partner than other TKIs that have failed in colorectal cancer, like lenvatinib and regorafenib, given that VEGF plays a crucial role in TME regulation through T cells, Treg, dendritic cells, and MDSCs.

Similar to the situation with regorafenib, the potential of fruquintinib in combination with cytotoxic chemotherapy is presently being studied in a number of clinical trials (Table 2) [15-29].

Table 2: On-going studies with fruquintinib in colorectal cancer [15–29].

	Clinical trial identifier	Phase	Treatment	Primary endpoint
First line	NCT01975077 [16]	II	FOLFOX/FOLFIRI and fruquintinib	PFS
Maintenance	NCT04296019 [17] NCT05016869 [18] NCT05451719 [19] NCT04733963 [20] NCT05659290 [21]	II or I/II	Fruquintinib or fruquintinib plus capecitabine	PFS
Second line	NCT05634590 [22]	II	FOLFOX/FOLFIRI and fruquintinib	PFS
	NCT05555901 [23]	II	FOLFIRI plus fruquintinib versus FOLFIRI plus bevacizumab	PFS
	NCT05522738 [24]	Ib/II	FOLFIRI and fruquintinib	ORR
	NCT05447715 [25]	II	Fruquintinib sequential bevacizumab plus FOLFIRI versus bevacizumab plus FOLFIRI sequential fruquintinib	PFS
Third line	NCT05004831 [26]	II	Fruquintinib and trifluridine/tipiracil	PFS
Chemorefractory	NCT04695470 [27]	II	Fruquintinib and sintilimab	PFS
	NCT04582981 [28]	II	Fruquintinib plus raltitrexed versus fruquintinib	PFS
	NCT04866862 [29]	II	Fruquintinib and camrelizumab	ORR

In patients with gastro-oesophageal cancer, regorafenib, a multitargeted kinase inhibitor that targets angiogenic and stromal receptor tyrosine kinases, has shown a slight advantage when used in conjunction with the 5-Fluorouracil and Oxaliplatin (FOLFOX) regimen [30].

When used with FTD/TPI, bevacizumab, another anti-angiogenic drug, induce blood vessels normalization, which raised the amount of FTD in tumours and produced the clinically significant benefit that led to FDA approval [31].

A combination of FTD/TPI and fruquintinib has emerged as a feasible option due to the prior benefit shown in the SUNLIGHT study (an open label, randomised, phase III study comparing trifluridine/tipiracil in combination with bevacizumab to trifluridine/tipiracil monotherapy in patients with refractory mCRC and the lack of overlapping toxicity [31].

Though worries about the possible toxicities are still unresolved, the promise of these combinations is evident given the significance of angiogenesis in the context of mCRC.

Fruquintinib as later line in metastatic colorectal cancer

The selection of third-line treatment for mCRC is still cause of debate. The safety and effectiveness of fruquintinib, regorafenib, and FTD/TPI have not been directly compared in clinical trials. The mCRC treatment in China at the time of the FRESCO trial differed from those outsides of the country [32].

No patients had received regorafenib or FTD/TPI, and only 30% had received VEGF-targeted therapy.

In contrast, the FRESCO-2 study required all patients to have either been intolerant to regorafenib or experienced disease progression on FTD/TPI, and more than 96% of patients had taken a VEGF inhibitor [7].

As a result, choosing the optimum course of treatment for patients who have not responded to at least two lines of systemic treatment remains challenging for clinicians. A meta-analysis of the CORRECT, CONCUR, RECOURSE, TERRA and FRESCO studies evaluating 2586 patients in total demonstrated that mOS and PFS were equal between fruquintinib and regorafenibe and between regorafenib and FTD/TPI. Instead fruquintinib compared to FDT/TPI obtained a superior PFS but similar OS [7,14,33-36].

The efficacy and toxicity profiles of fruquintinib and regorafenib were similar in a few Chinese retrospective trials however, the OS was longer for regorafenib followed by fruquintinib than for the opposite treatment sequence [37,38].

Nevertheless, a meta-analysis comprising three randomised studies and 1,380 patients revealed no difference in grade 3–5 events (OR 0.92; 95% CI 0.64–1.32), but a significant difference in all-grade toxicity when fruquintinib was compared to regorafenib (Odds Ratio [OR] 0.73; 95% CI 0.65–0.82) [39]. The better selectivity of fruquintinib in reducing angiogenesis may be the cause of this difference in reduced toxicity. To identify the best course of treatment, more clinical research will be required.

Conclusions

Phase III trials have shown strong evidence that fruquintinib is a new standard treatment for refractory mCRC, highlighting neoangiogenesis as one of the most important processes for cancer growth.

Although every attempt should be made to find clinical and molecular biomarkers that predict response, research with lower doses should be promoted because regorafenib toxicity was noticeable in a comparable situation.

Last but not least, given the TME modulation, fruquintinib presents a strong case for combination with various ICIs and cytotoxic chemotherapy; numerous trials are currently investigating these combinations.

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