Efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer with and without liver metastasis: A subgroup analysis of the phase 3 FRESCO-2 trial

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Background

- In colorectal cancer (CRC), the liver is the most common site of metastasis,[1] with up to half of all patients with CRC developing liver metastases during their disease course[2]
- Prognosis is poor for patients with metastatic CRC (mCRC) who have liver metastases, with an estimated 5-year survival rate of 14%[3]
- Fruquintinib is a highly selective oral inhibitor of all three vascular endothelial growth factor receptors (VEGFRs -1, -2, and -3)[4]
- Following results from the phase 3 FRESCO (NCT02314819) and FRESCO-2 studies (NCT04322539),[5,6] fruquintinib was approved in the US and Europe for previously treated mCRC[7,8]
- In FRESCO-2, fruquintinib + best supportive care (BSC) versus placebo + BSC demonstrated significantly improved overall survival (OS; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.55–0.80; p<0.001) and progression-free survival (PFS; HR 0.32, 95% CI 0.27–0.39; p<0.001), with a manageable safety profile consistent with the previously established monotherapy profile[6]
- This subgroup analysis investigated the efficacy and safety of fruquintinib in patients from FRESCO-2 with and without liver metastases

Methods

- The study design is outlined in the summary panel, and has been described in detail previously[6]
- This analysis of a predefined subgroup evaluated efficacy and safety, focusing on hepatic function abnormality, according to the presence and absence of liver metastases at baseline
- OS and PFS were evaluated by the Kaplan–Meier method with differences tested using the log-rank test; survival HRs were estimated using a Cox proportional hazards model[6]
- Treatment emergent adverse events (TEAEs) were coded according to MedDRA (version 25.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0)
- Time to deterioration (TTD) of Eastern Cooperative Oncology Group performance status (ECOG PS) was investigated via Kaplan–Meier analysis of time (months) from randomization to first occurrence of ECOG PS ≥2 or death within the safety follow-up (30 +/-7 days of last dose)

Results

Patients

- Overall, 339 of 461 (73.5%) patients randomized to fruquintinib and 156 of 230 (67.8%) patients randomized to placebo had liver metastases
- Baseline demographics and disease characteristics are shown in **Table 1**

Table 1. Baseline characteristics in the fruquintinib and placebo arms according to the presence and absence of liver metastases at baseline (ITT population)

Characteristic	Patients with liver metastases at baseline		Patients without liver metastases at baseline	
	Fruquintinib (n=339)	Placebo (n=156)	Fruquintinib (n=122)	Placebo (n=74)
Median age, years (range)	63.0 (25, 81)	64.0 (35, 86)	64.0 (32, 82)	64.5 (30, 77)
Male, %	53.7	66.0	51.6	50.0
ECOG PS, %				
0	40.4	40.4	48.4	52.7
1	59.6	59.6	51.6	47.3
Primary site at first diagnosis, %				
Colon, left	42.2	41.7	40.2	36.5
Colon, right	20.9	26.3	21.3	16.2
Colon, other*	6.8	5.8	4.9	8.1
Rectum	30.1	26.3	33.6	39.2
Number of prior treatment lines for metastatic disease, %				
≤3	26.8	29.5	27.9	24.3
>3	73.2	70.5	72.1	75.7
Median duration of metastatic disease				
≤18 months, %	9.1	5.1	4.9	6.8
>18 months, %	90.9	94.9	95.1	93.2
***RAS* mutation-positive, %**	61.9	60.9	66.4	67.6
***BRAF* mutation-positive, %**	10.9	10.9	18.9	20.3
MSI-H and/or dMMR, %	0.6	1.3	2.5	2.7
Prior treatment, %				
VEGF inhibitor	96.5	96.2	96.7	95.9
EGFR inhibitor	40.7	39.7	34.4	35.1
Trifluridine/tipiracil	52.2	49.4	51.6	59.5
Regorafenib	8.8	8.3	8.2	6.8
Trifluridine/tipiracil and regorafenib	38.9	42.3	40.2	33.8

*'Colon other' includes 'Colon, left and right', and 'Colon, unknown'. dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; ITT, intent-to-treat; MSI-H, microsatellite instability high

Question — **Does the efficacy and safety of fruquintinib versus placebo in patients with refractory mCRC differ according to the presence or absence of liver metastases at baseline?**

Study design

FRESCO-2:
Patients with mCRC from North America, Europe, Japan, and Australia (**N=691**)

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Fruquintinib (n=461)
5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

Placebo (n=230)
5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

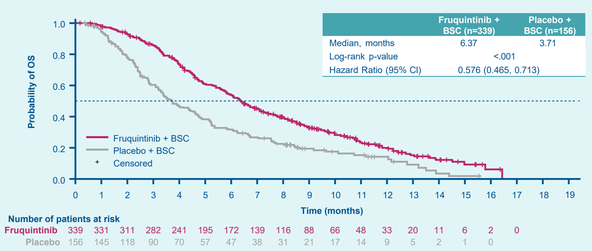
Treatment until PD or unacceptable toxicity

Primary endpoint: OS
Secondary endpoints: PFS, ORR, DCR, and safety
Post hoc: Time to ECOG PS worsening

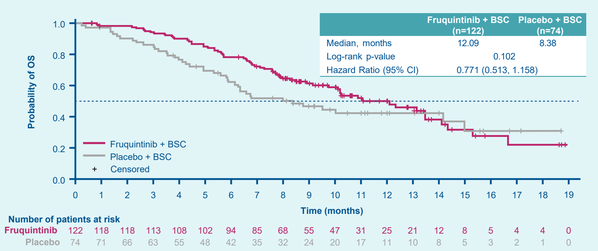
Subgroup analysis:
Liver metastases at baseline: fruquintinib (n=339); placebo (n=156)
No liver metastases at baseline: fruquintinib (n=122); placebo (n=74)

Figure 1. OS in the fruquintinib and placebo arms according to the presence and absence of liver metastases at baseline (ITT population)

Patients with liver metastases



Patients without liver metastases

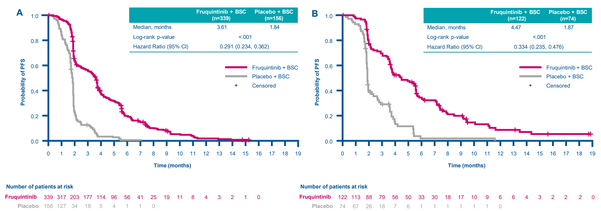


Key conclusions — **Fruquintinib was associated with consistent efficacy improvements and tolerability compared with placebo in patients with refractory mCRC, regardless of liver metastasis status at baseline**

Efficacy outcomes

- Improvements in OS with fruquintinib versus placebo were observed regardless of the presence or absence of liver metastases (**Summary Panel; Figure 1**)
  - In patients with liver metastases, median OS was 6.4 months with fruquintinib and 3.7 months with placebo (HR 0.58; 95% CI 0.47–0.71; p<0.001)
  - In patients without liver metastases, median OS was 12.1 months with fruquintinib and 8.4 months with placebo (HR 0.77; 95% CI 0.51–1.16; p=0.102)
- Median PFS was also longer with fruquintinib compared with placebo, with improvements of 1.8 months (HR 0.29; 95% CI 0.23–0.36; p<0.001) and 2.6 months (HR 0.33; 95% CI 0.24–0.48; p<0.001) seen in patients with and without liver metastases, respectively (**Figure 2**)

Figure 2. PFS in the fruquintinib and placebo arms according to the A) presence and B) absence of liver metastases at baseline (ITT population)



- The disease control rate (DCR) was higher with fruquintinib versus placebo in patients with liver metastases (53% versus 8%) and without liver metastases (64% versus 32%) (**Table 2**)

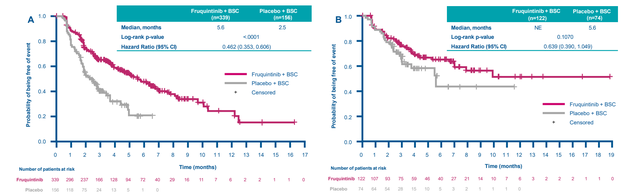
Table 2. Response rates in the fruquintinib and placebo arms according to the presence and absence of liver metastases at baseline (ITT population)

n (%)	Patients with liver metastases at baseline		Patients without liver metastases at baseline	
	Fruquintinib (n=339)	Placebo (n=156)	Fruquintinib (n=122)	Placebo (n=74)
ORR (CR+PR)	**2 (0.6)**	**0**	**5 (4.1)**	**0**
Best overall response				
CR	0	0	0	0
PR	2 (0.6)	0	5 (4.1)	0
SD	176 (51.9)	13 (8.3)	73 (59.8)	24 (32.4)
PD	110 (32.4)	103 (66.0)	29 (23.8)	40 (54.1)
Not evaluable	3 (0.9)	1 (0.6)	3 (2.5)	0
NA	48 (14.2)	39 (25.0)	12 (9.8)	10 (13.5)
DCR (CR+PR+SD*)†	178 (52.5)	13 (8.3)	78 (63.9)	24 (32.4)
P-value‡	<0.0001		<0.0001	

*For at least 7 weeks; †p<0.0001 fruquintinib versus placebo for patients with or without liver metastases; ‡Two-sided p-value calculated using the Cochran-Mantel Hanzel method. CR, complete response; NA, not applicable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

- In patients with liver metastases, the median TTD to ECOG PS of ≥2 or death within the safety follow-up (30 +/-7 days after the last dose) was 5.6 months with fruquintinib versus 2.5 months with placebo (adjusted HR 0.46; 95% CI 0.35–0.61; p<0.0001, **Figure 3**)
  - In patients without liver metastases, the corresponding median times were not reached versus 5.6 months (HR 0.64; 95% CI 0.39–1.0; p=0.1070, **Figure 3**)

Figure 3. TTD to ECOG PS ≥2 or death within the safety follow-up in the fruquintinib and placebo arms according to the A) presence and B) absence of liver metastases at baseline (ITT population)



Safety outcomes

- In patients receiving fruquintinib, rates of TEAEs of any grade and grade ≥3, as well as serious TEAEs were similar regardless of whether patients had liver metastases (**Table 3**)
- Hepatic function abnormalities was a predefined adverse event of special interest category
  - While rates of grade ≥3 hepatic function abnormalities were comparable with fruquintinib versus placebo in patients with liver metastases, higher rates were reported with fruquintinib versus placebo in patients without liver metastases (**Table 3**)
  - Rates of hepatic function laboratory abnormalities are summarized in **Table 4**
    - Overall, four patients (one in the fruquintinib group who did not have metastases and three in the placebo arm who had metastases) met Hy's Law laboratory criteria (**Table 4**)

Table 3. Safety overview and grade ≥3 TEAEs occurring in ≥5% of patients in the fruquintinib and placebo arms according to the presence and absence of liver metastases at baseline (safety population)*

n (%)	Patients with liver metastases at baseline		Patients without liver metastases at baseline	
	Fruquintinib (n=335)	Placebo (n=155)	Fruquintinib (n=121)	Placebo (n=75)
Any-grade TEAE	**331 (98.8)**	**145 (93.5)**	**120 (99.2)**	**68 (90.7)**
Grade ≥3	213 (63.6)	83 (53.5)	73 (60.3)	33 (44.0)
Serious TEAE	**125 (37.3)**	**63 (40.6)**	**46 (38.0)**	**25 (33.3)**
Grade ≥3	117 (34.9)	61 (39.4)	45 (37.2)	24 (32.0)
Treatment-related TEAE	291 (86.9)	88 (56.8)	104 (86.0)	42 (56.0)
Grade ≥3	122 (36.4)	19 (12.3)	42 (34.7)	7 (9.3)
TEAE leading to death	**40 (11.9)**	**37 (23.9)**	**8 (6.6)**	**8 (10.7)**
Treatment-related	1 (0.3)†	1 (0.6)†	0	0
Grade ≥3 TEAEs in ≥5% of patients				
Hypertension	**40 (11.9)**	**1 (0.6)**	**22 (18.2)**	**1 (1.3)**
Hepatic function abnormalities‡	**34 (10.1)**	**20 (12.9)**	**4 (3.3)**	**1 (1.3)**
Asthenia	**32 (9.6)**	**9 (5.8)**	**3 (2.5)**	**0**
PPE	**19 (5.7)**	**0**	**10 (8.3)**	**0**
Fatigue	**12 (3.6)**	**2 (1.3)**	**6 (5.0)**	**0**
Anemia	**3 (0.9)**	**2 (1.3)**	**2 (1.7)**	**5 (6.7)**

*Of 5 patients assigned to fruquintinib, 3 did not receive fruquintinib, and 2 received placebo instead; 2 patients assigned to placebo did not receive treatment.
†Of the deaths that were deemed treatment-related, 1 was due to intestinal perforation in the fruquintinib arm, and 1 was due to cardiac arrest in the placebo arm.
‡AESI category encompassing all preferred term hepatic abnormalities, including laboratory abnormalities. PPE, palmar-plantar erythrodysesthesia.

Table 4. Summary of hepatic laboratory abnormalities in the fruquintinib and placebo arms according to the presence and absence of liver metastases at baseline (safety population)*

n (%)	Patients with liver metastases at baseline		Patients without liver metastases at baseline	
	Fruquintinib (n=335)	Placebo (n=155)	Fruquintinib (n=121)	Placebo (n=75)
AST or ALT >3x ULN	**79 (23.6)**	**38 (24.5)**	**13 (10.7)**	**5 (6.7)**
Total bilirubin >2x ULN	**43 (12.8)**	**24 (15.5)**	**5 (4.1)**	**0**
AST/ALT >3x and bilirubin >2x ULN	**24 (7.2)**	**17 (11.0)**	**3 (2.5)**	**0**
Hy's Law laboratory criteria†	**0**	**3 (1.9)**	**1 (0.8)**	**0**

*Of 5 patients assigned to fruquintinib, 3 did not receive fruquintinib, and 2 received placebo instead; 2 patients assigned to placebo did not receive treatment.
†AST/ALT >3x ULN, total bilirubin >2x ULN and alkaline phosphatase <2x ULN. ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Conclusions

- The results of this analysis demonstrated longer survival with fruquintinib compared with placebo in this heavily pretreated population of patients with mCRC, regardless of the presence of liver metastases at baseline
  - Irrespective of treatment, patients with liver metastases at baseline had shorter median OS than those without liver metastases, indicating a poorer prognosis
- In both subgroups, the time to ECOG PS ≥2 or death was longer in patients who received fruquintinib compared with placebo
- The incidence and severity of hepatic AEs were both generally comparable between treatment arms in patients with liver metastases at baseline
- Fruquintinib is an effective and tolerable treatment option for patients with mCRC regardless of liver metastases

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Disclosures

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