Safety and tolerability of fruquintinib: Pooled analysis of three placebo-controlled studies in patients with metastatic colorectal cancer

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Background

- Fruquintinib, a highly selective, oral inhibitor of all three vascular endothelial growth factor receptors (VEGFRs -1, -2, and -3), is approved for the treatment of refractory metastatic colorectal cancer (mCRC), including in the United States,[1] Europe,[2] and China[3]
- Approvals were based on the results of the phase 3 FRESCO (NCT02314819) and FRESCO-2 (NCT04322539) studies, which both met their primary endpoints by demonstrating a significant overall survival (OS) benefit with fruquintinib plus best supportive care (BSC) versus placebo plus BSC[4,5]
  - In the fruquintinib arm versus the placebo arm, FRESCO demonstrated a median OS of 9.3 versus 6.6 months (hazard ratio [HR]: 0.65; 95% confidence interval [CI]: 0.51−0.83; *P*<0.001),[4] and FRESCO-2 demonstrated a median OS of 7.4 versus 4.8 months (HR: 0.66; 95% CI: 0.55−0.80; *P*<0.001)[5]
- The cumulative toxicity burden associated with multiple lines of treatment can be high for patients with refractory mCRC;[6] therefore, it is important for treatments with proven efficacy to also be tolerable and have manageable safety profiles, to ensure doses can be maintained
- Treatment with VEGFR inhibitors specifically has been shown to be associated with certain treatment-emergent adverse events (TEAEs) including hypertension, proteinuria, and palmar plantar erythrodysesthesia (PPE)[7]
- We report a pooled safety analysis of prespecified adverse events of special interest (AESIs) from FRESCO, FRESCO-2, and a phase 2 placebo-controlled study (NCT02196688),[8] all of which investigated the efficacy and safety of fruquintinib in patients with mCRC

Methods

- The study designs of FRESCO, FRESCO-2, and the phase 2 study are outlined in the summary panel, and have been described in detail previously[4,5,8]
  - In all three studies, patients with refractory mCRC were randomized 2:1 to receive fruquintinib 5 mg or matching placebo, plus BSC, until progressive disease (PD) or unacceptable toxicity
  - In FRESCO and the phase 2 study, eligible patients had received ≥2 prior chemotherapy regimens, which could have included prior anti-vascular endothelial growth factor (VEGF) and/or anti-epidermal growth factor receptor (EGFR) therapies
  - In FRESCO-2, eligible patients had received prior standard chemotherapy, anti-VEGF and anti-EGFR therapies if indicated, and prior TAS-102 and/or regorafenib
- All patients included in the safety populations of each study (defined as patients who received ≥1 dose of study treatment)[4,5,8] were included in this pooled analysis
- For all studies, TEAEs were coded using the Medical Dictionary for Regulatory Activities Version 25.0 (MedDRA v25.0)[9] and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0)[10]
  - For FRESCO and the phase 2 study, TEAEs were evaluated from the first dose of study treatment to 30 days after the end of treatment[4,8]
  - For FRESCO-2, TEAEs were evaluated from the first dose of study treatment to 30 ±7 days after the end of treatment, or start of a new anti-tumor treatment (whichever occurred first)[11]
- AESIs were prespecified based on the VEGFR tyrosine kinase inhibitor drug class and were classified into the following 10 categories according to MedDRA v25.0 terms

Dermatological toxicity · **Hypertension** · **Embolic and thrombotic events** · **Infection** · **Gastrointestinal perforation** · **Decreased left ventricular ejection fraction** · **Hemorrhage** · **Proteinuria** · **Hepatic function abnormal** · **Thyroid dysfunction**

- Within these AESI categories, prespecified preferred terms were also assessed
- Patients were closely monitored, and AESIs were managed via dose modification and supportive treatments
- This analysis evaluated AESIs for frequency, time to first onset, and time to resolution

Results

Patients

- Across all three studies, 786 versus 392 patients were randomized to receive fruquintinib versus placebo[4,5,8]
- Of all patients randomized to receive fruquintinib and placebo, respectively, 5 patients and 1 patient did not receive assigned study treatment, and were excluded from the relevant safety populations[4,5,8]
- Therefore, the pooled cohort analyzed here included 781 patients (66.6%) who received fruquintinib, and 391 patients (33.4%) who received placebo (**Table 1**)
  - Baseline characteristics were generally similar with fruquintinib versus placebo, although a lower proportion of patients in the fruquintinib group were male (55.6% vs 64.7%)
  - Across all studies, patients received a median of four prior lines of treatment for metastatic disease

Safety outcomes

- As expected, evaluated AESIs were experienced by 86.7% of patients in the fruquintinib group (grade ≥3: 40.6%) and 58.3% of patients in the placebo group (grade ≥3: 16.1%; **Table 2**)
- The AESI categories with the highest incidence in the fruquintinib group were hypertension, dermatological toxicity, and abnormal hepatic function, which all had a median time to onset of <30 days with both fruquintinib and placebo (**Summary Panel, Figure 1**)

Question What are the safety and tolerability outcomes with fruquintinib + BSC versus placebo + BSC in patients with refractory mCRC, based on a pooled analysis of three clinical studies?

Study design

FRESCO (N=416)
FRESCO-2 (N=691)
NCT02196688 (N=71)

R 2:1

Fruquintinib (n=786)	
FRESCO: n=278 FRESCO-2: n=461 NCT02196688: n=47	5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)
Placebo (n=392)	
FRESCO: n=138 FRESCO-2: n=230 NCT02196688: n=24	5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

Treatment until PD or unacceptable toxicity

Safety analysis of AESIs in the pooled safety population (N=1,172)

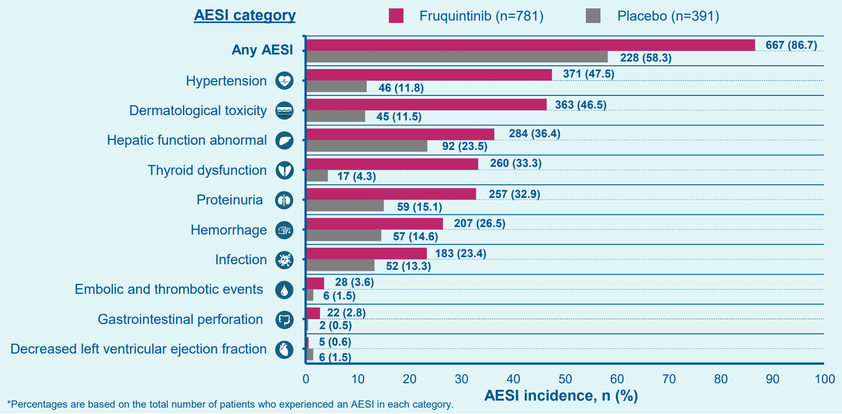
Fruquintinib: n=781
Placebo: n=391

For all studies, TEAEs were coded using MedDRA v25.0 and graded according to NCI-CTCAE v5.0

AESIs were prespecified based on VEGFR tyrosine kinase inhibitor class drugs

Analyses included:
- AESI incidence
- Median time to AESI onset
- Median time to AESI resolution

Figure 1: Incidence, median time to onset, and median time to resolution for each any-grade AESI category analysed with fruquintinib versus placebo



Median time to onset, days	Median time to resolution, days	Patients with resolved AESIs, n (%)*
12.0	**36.0**	**161 (24)**
21.0	24.0	79 (35)
15.0	**22.0**	**187 (50)**
16.0	15.0	24 (52)
19.0	**36.0**	**219 (60)**
17.0	24.0	29 (64)
28.0	**17.0**	**96 (34)**
22.0	14.0	21 (23)
56.0	**31.0**	**59 (23)**
56.0	29.0	5 (29)
28.0	**18.0**	**131 (51)**
25.0	14.0	29 (49)
23.0	**12.0**	**149 (72)**
19.0	12.0	34 (60)
52.0	**10.0**	**120 (66)**
31.5	8.0	34 (65)
78.5	**7.5**	**11 (39)**
39.5	10.0	2 (33)
53.5	**22.0**	**15 (68)**
40.0	21.0	1 (50)
33.0	**16.0**	**2 (40)**
28.0	15.0	1 (17)

*Percentages are based on the total number of patients who experienced an AESI in each category.

Key conclusions Despite study protocol and population differences, AESIs were consistent with the mechanism of action of fruquintinib. Most patients were able to maintain the fruquintinib 5 mg starting dose, and discontinuation rates due to AESIs were low. These data support fruquintinib as an effective, tolerable treatment option in patients with refractory mCRC.

Table 1: Baseline characteristics with fruquintinib versus placebo

Characteristic	Pooled cohort (N=1,172)	
	Fruquintinib (n=781)	Placebo (n=391)
Median age, years (range)	60.0 (23–82)	62.0 (24–86)
Male, n (%)	434 (55.6)	253 (64.7)
Race, n (%)		
Asian	367 (47.0)	180 (46.0)
White	364 (46.6)	190 (48.6)
Black or African American	13 (1.7)	7 (1.8)
Other	37 (4.7)	14 (3.6)
ECOG PS, n (%)		
0	276 (35.3)	143 (36.6)
1	505 (64.7)	248 (63.4)
Site at first diagnosis, n (%)		
Colon	447 (57.2)	220 (56.3)
Rectum	289 (37.0)	140 (35.8)
Colon and rectum	45 (5.8)	30 (7.7)
Unknown	0	1 (0.3)
Duration of metastatic disease, n (%)		
≤18 months	220 (28.2)	101 (25.8)
>18 months	561 (71.8)	290 (74.2)
Prior number of treatment lines for metastatic disease		
Median, n (range)	4.0 (2−16)	4.0 (2−14)
≤3, n (%)	293 (37.5)	156 (39.9)
>3, n (%)	488 (62.5)	235 (60.1)
***RAS* mutation-positive, n (%)**	408 (52.2)	209 (53.5)
Select prior treatment, n (%)		
VEGF inhibitor	524 (67.1)	262 (67.0)
EGFR inhibitor	219 (28.0)	106 (27.1)

ECOG PS, Eastern Cooperative Oncology Group performance status.

- With fruquintinib versus placebo, hypertension resolved in 50% versus 52% of patients, dermatological toxicity resolved in 60% versus 64% of patients, and abnormal hepatic function resolved in 34% versus 23% of patients who experienced AESIs in each category (**Summary Panel, Figure 1**)
  - The median time to resolution for AESIs in each category was generally similar with fruquintinib and placebo
  - Only dermatological toxicity and thyroid disfunction had a median time to resolution of >30 days in the fruquintinib group

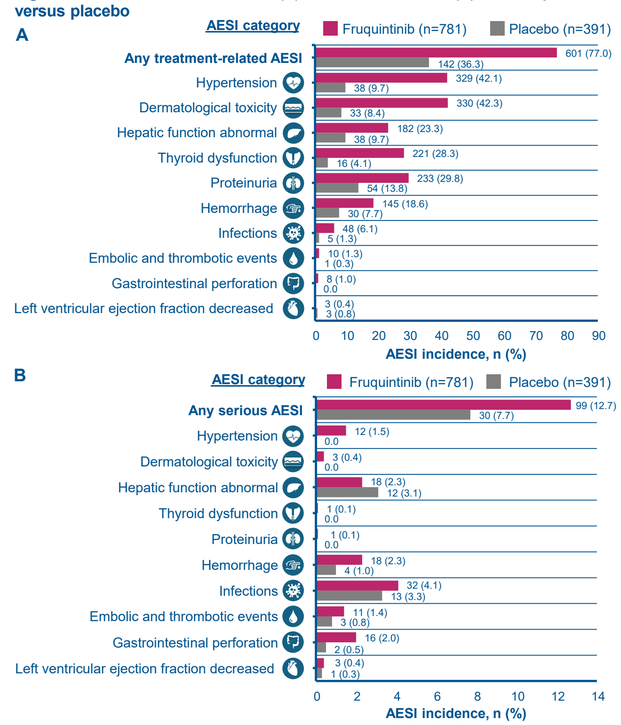
Table 2: Any-grade and grade ≥3 AESIs with fruquintinib versus placebo

AESI Category, n (%) Preferred term, n (%)*	Pooled cohort (N=1,172)			
	Fruquintinib (n=781)		Placebo (n=391)	
	Any-grade	Grade ≥3	Any-grade	Grade ≥3
Any AESI	677 (86.7)	317 (40.6)	228 (58.3)	63 (16.1)
Hypertension	**371 (47.5)**	**144 (18.4)**	**46 (11.8)**	**5 (1.3)**
Hypertension	349 (44.7)	134 (17.2)	44 (11.3)	5 (1.3)
Dermatological toxicity	**363 (46.5)**	**69 (8.8)**	**45 (11.5)**	**1 (0.3)**
PPE	255 (32.7)	66 (8.5)	12 (3.1)	0
Rash	50 (6.4)	0	10 (2.6)	1 (0.3)
Hepatic function abnormal	**284 (36.4)**	**69 (8.8)**	**92 (23.5)**	**37 (9.5)**
AST increased	141 (18.1)	14 (1.8)	39 (10.0)	6 (1.5)
ALT increased	121 (15.5)	16 (2.0)	25 (6.4)	3 (0.8)
Bilirubin increased	116 (14.9)	21 (2.7)	35 (9.0)	16 (4.1)
GGT increased	35 (4.5)	9 (1.2)	13 (3.3)	6 (1.5)
Hepatic function abnormal	28 (3.6)	12 (1.5)	6 (1.5)	2 (0.5)
Thyroid dysfunction	**260 (33.3)**	**2 (0.3)**	**17 (4.3)**	**0**
Hypothyroidism	143 (18.3)	2 (0.3)	4 (1.0)	0
TSH increased	114 (14.6)	0	7 (1.8)	0
Proteinuria	**257 (32.9)**	**22 (2.8)**	**59 (15.1)**	**2 (0.5)**
Proteinuria	222 (28.4)	18 (2.3)	52 (13.3)	2 (0.5)
Protein urine present	34 (4.4)	3 (0.4)	7 (1.8)	0
Hemorrhage	**207 (26.5)**	**16 (2.0)**	**57 (14.6)**	**4 (1.0)**
Occult blood positive	55 (7.0)	1 (0.1)	14 (3.6)	0
Epistaxis	44 (5.6)	0	5 (1.3)	0
Haematuria	28 (3.6)	1 (0.1)	13 (3.3)	1 (0.3)
Infection	**183 (23.4)**	**47 (6.0)**	**52 (13.3)**	**15 (3.8)**
UTI	47 (6.0)	6 (0.8)	16 (4.1)	4 (1.0)
URTI	25 (3.2)	1 (0.1)	4 (1.0)	0
Embolic and thrombotic events	**28 (3.6)**	**17 (2.2)**	**6 (1.5)**	**3 (0.8)**
Gastrointestinal perforation	**22 (2.8)**	**15 (1.9)**	**2 (0.5)**	**2 (0.5)**
LVEF decreased	**5 (0.6)**	**4 (0.5)**	**6 (1.5)**	**2 (0.5)**

*TEAEs that affected >3% of patients in the fruquintinib group.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; LVEF, left ventricular ejection fraction; TSH, thyroid stimulating hormone; URTI, upper respiratory tract infection; UTI, urinary tract infection.

- The incidence of AESIs that were considered to be treatment-related or serious are summarized in **Figure 2**
  - Treatment-related AESIs occurred in 77% versus 36% of patients with fruquintinib versus placebo
    - The most common treatment-related AESIs were dermatological toxicity, hypertension, and proteinuria in the fruquintinib group, and proteinuria, hepatic function abnormal, and hypertension in the placebo group
  - Serious AESIs occurred in 13% and 8% of patients with fruquintinib versus placebo, the most common being infections in both the fruquintinib and placebo groups

Figure 2: Treatment-related AESIs* (A) and serious AESIs† (B) with fruquintinib versus placebo



*Treatment-related TEAEs were defined as events that were considered to be causally related to study drug treatment.
†Serious TEAEs were defined as events that resulted in substantial incapacity, hospitalization, or death.

- Median relative dose intensity (interquartile range) was 95.9% (83.3−100.0) in the fruquintinib group, and 100% (92.8−100.0) in the placebo group
- The proportion of patients who experienced any-grade and grade ≥3 AESIs leading to dose modifications, with fruquintinib versus placebo, are summarized in **Table 3**
- In total, 17 patients (2.2%) in the fruquintinib group, and 5 patients (1.3%) in the placebo group, experienced AESIs that led to death
  - These were treatment-related in 6 patients (0.8%) and 1 patient (0.3%), respectively

Table 3: AESIs leading to dose modifications with fruquintinib versus placebo

Dose modification, n (%)	Pooled cohort (N=1,172)	
	Fruquintinib (n=781)	Placebo (n=391)
Any AESIs leading to dose reduction*	124 (15.9)	6 (1.5)
Grade ≥3	75 (9.6)	3 (0.8)
Any AESIs leading to dose interruption*	186 (23.8)	39 (10.0)
Grade ≥3	99 (12.7)	14 (3.6)
Any AESIs leading to treatment discontinuation*	69 (8.8)	19 (4.9)
Grade ≥3	55 (7.0)	15 (3.8)

*Patient numbers for any AESIs are not additive; one patient could have a dose reduction, dose interruption, and treatment discontinuation.

Conclusions

- The overall safety profile of fruquintinib was consistent with each of the individual studies included in this pooled analysis, and no new safety signals were identified[4,5,8]
- Despite study protocol and population differences, AESIs were generally low-grade with fruquintinib and placebo, and could be managed with dose modifications and/or supportive care
- The time to AESI resolution was generally similar in both the fruquintinib and placebo groups
- Most patients were able to maintain the fruquintinib 5 mg starting dose, and discontinuation rates due to AESIs were low
- Overall, these data support fruquintinib as a tolerable treatment option in patients with refractory mCRC

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