Analysis of fruquintinib adverse events of special interest from phase 3 FRESCO-2 study

Poster 301

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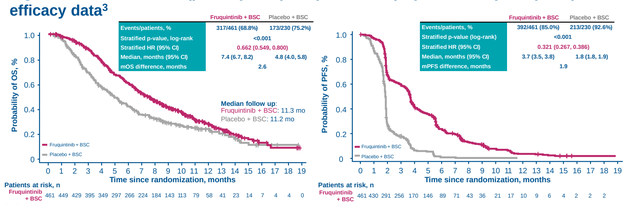
BACKGROUND

- Fruquintinib is a highly selective and potent inhibitor of all 3 VEGF receptors (VEGFR-1, -2, and -3) with weak or no inhibitory effect on other receptor kinases[1]
- Fruquintinib is approved in China in patients with metastatic colorectal cancer (mCRC) as ≥3rd line therapy based on results from the phase 3 FRESCO study (NCT02314819) conducted in China[2]
- The global phase 3 FRESCO-2 study (NCT04322539) randomized 691 patients and was conducted in the US, Europe, Japan, and Australia in more heavily pretreated patients with mCRC compared with FRESCO, reflecting current global practices
- In FRESCO-2, fruquintinib (plus best supportive care [BSC]) demonstrated statistically significant and clinically meaningful improvements in overall survival (OS) and progression-free survival (PFS) **(Figure 1)** vs placebo + BSC, as well as a favorable safety profile[3], along with no deterioration in quality of life[4]
- Here we report the treatment emergent adverse events of special interest (AESIs) identified and reported with fruquintinib + BSC and placebo + BSC in FRESCO-2 to further characterize the safety profile of fruquintinib

Figure 1: FRESCO-2 OS (primary endpoint) and PFS (key secondary endpoint) efficacy data[3]



METHODS

- Eligible patients had received all standard treatments, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, anti-VEGF therapy, anti-EGFR therapy (if RAS wild type) and had progressed on, or been intolerant to, trifluridine/tipiracil or regorafenib
  - Patients with MSI-high or MMR-deficient tumors or BRAFV600E-mutant tumors must have also received an immune checkpoint inhibitor or BRAF inhibitor
- Treatment-emergent AESIs were defined as AEs in patients who had received at least one dose of study drug, with an onset during receipt of study treatment, and up to 30 days after end of treatment; AESIs constitute the 10 following categories: dermatologic toxicity, hypertension, thyroid dysfunction, proteinuria, liver function test abnormality, hemorrhages, infections, embolic and thrombotic events, gastrointestinal perforation, and left ventricular ejection fraction decreased
  - These treatment-emergent AESIs were further filtered by the respective MedDRA SMQ search criteria defined in the investigator brochure
  - Selected AESIs based on VEGFR tyrosine kinase inhibitor drug classes were evaluated for frequency, time to first onset, and frequency over time

RESULTS

Patients

- The safety population included 686 patients who received at least one dose of study drug; all results presented here are based on the safety population
- Baseline demographics and disease characteristics were well balanced between treatment arms **(Table 1)**

Table 1: Baseline demographics and disease characteristics

Characteristics, n (%)*		Fruquintinib + BSC (n=456)	Placebo + BSC (n=230)
Age, years	Median (range)	64 (56, 70)	64 (57, 69)
	≥65	212 (46.5)	112 (48.7)
Sex	Female	215 (47.1)	90 (39.1)
	Male	241 (52.9)	140 (60.9)
ECOG PS	0	193 (42.3)	102 (44.3)
	1	263 (57.7)	128 (55.7)
Liver metastases	Yes	335 (73.5)	155 (67.4)
Prior therapies	Anti-VEGF	440 (96.5)	221 (96.1)
	Anti-EGFR	179 (39.3)	88 (38.3)
Prior TAS-102 and/or regorafenib	TAS-102	237 (52.0)	121 (52.6)
	Regorafenib	40 (8.8)	18 (7.8)
	Both	179 (39.3)	91 (39.6)
Number of prior treatment lines in metastatic disease	Median (range)	4 (2–16)	4 (2–12)
	≤3	124 (27.2)	64 (27.8)
	>3	332 (72.8)	166 (72.2)

*Unless otherwise stated. ECOG PS, Eastern Cooperative Oncology Group performance status

Question

What are the treatment-emergent adverse events of special interest (AESIs) reported with fruquintinib + BSC vs placebo + BSC in the FRESCO-2 trial in heavily pretreated patients with mCRC and existing comorbidities?

Study design

FRESCO-2
(NCT04322539)

Global, multicenter, randomized, placebo-controlled phase 3 study

Fruquintinib 5 mg PO QD (3 weeks on, 1 week off) + BSC

2:1

Placebo 5 mg PO QD (3 weeks on, 1 week off) + BSC

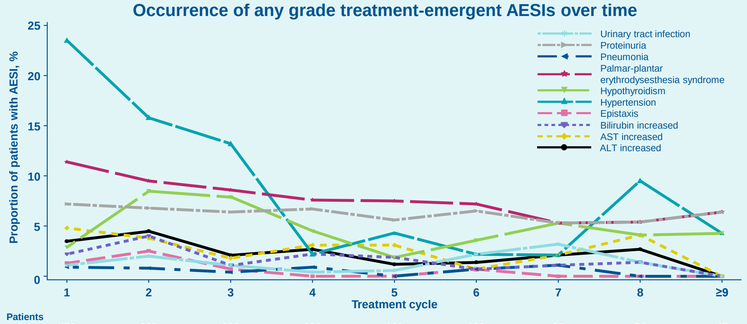
Endpoints:
- **Primary:** OS
- **Key secondary:** PFS
- **Other secondary:** Overall response rate, disease control rate, safety

AEs were coded using MedDRA v25.0 and graded by NCI-CTCAE v5.0.

Clinically relevant class toxicities were grouped into respective AESI categories

Key results

Occurrence of any grade treatment-emergent AESIs over time



Key take aways

Fruquintinib + BSC had a manageable safety profile, and AESIs including hypertension, palmar-plantar erythrodysesthesia syndrome, and proteinuria were well managed with appropriate monitoring and treatment

- Comparing patients who received fruquintinib + BSC with patients who received placebo + BSC, patients with any medical history were reported in 430 (94.3%) vs 222 (96.5%), respectively
- The most frequently reported medical history **(Table 2)** of patients included hypertension (50.6%) at baseline along with hypothyroidism (7.6%), proteinuria (3.1%), and palmar-plantar erythrodysesthesia syndrome (1.7%)

Table 2: Relevant medical history reported at study entry

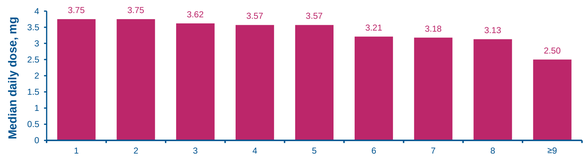
PT, n (%)	Fruquintinib + BSC (n=456)	Placebo + BSC (n=230)
Hypertension	227 (49.8)	120 (52.2)
Hypothyroidism	34 (7.5)	18 (7.8)
Proteinuria	17 (3.7)	4 (1.7)
Palmar-plantar erythrodysesthesia syndrome	9 (2.0)	3 (1.3)
Infections*	65 (14.3)	38 (16.5)
Investigations†	46 (10.1)	24 (10.4)

*Includes PT urinary tract infection; †includes PTs AST increased, ALT increased and blood bilirubin increase
ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT, preferred term

Dose intensity

- The median duration of exposure was greater with fruquintinib (3.06 months, range 1.84–5.55) than with placebo (1.84 months, range 0.95–2.27)
- Daily target dose of fruquintinib was 3.75 mg; median daily fruquintinib dose by treatment cycle is shown in **Figure 2**

Figure 2: Median daily fruquintinib dose by treatment cycle



Treatment-emergent AESIs

- Comparing patients who received fruquintinib + BSC with patients who received placebo + BSC, any grade AESIs were reported in 368 (80.7%) vs 122 (53%) patients; and grade ≥3 AESIs were reported in 169 (37.1%) vs 44 (19.1%) patients, respectively **(Table 3)**

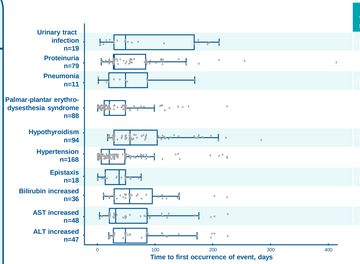
Table 3: Treatment-emergent AESIs (any grade, PT occurring in ≥5% patients)

AESI category, n (%)* PT	Fruquintinib + BSC (n=456)		Placebo + BSC (n=230)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension†	179 (38.4)	65 (14.0)	20 (8.7)	2 (0.9)
Hypertension	168 (36.8)	62 (13.6)	20 (8.7)	2 (0.9)
Dermatological toxicity	157 (34.4)	31 (6.8)	27 (11.7)	1 (0.4)
Palmar-plantar erythrodysesthesia syndrome	88 (19.3)	29 (6.4)	6 (2.6)	0
Liver function test abnormality	113 (24.8)	38 (8.3)	44 (19.1)	21 (9.1)
AST increased	48 (10.5)	10 (2.2)	11 (4.8)	3 (1.3)
ALT increased	47 (10.3)	14 (3.1)	9 (3.9)	1 (0.4)
Blood bilirubin increased	36 (7.9)	11 (2.4)	11 (4.8)	6 (2.6)
Thyroid dysfunction	123 (27.0)	2 (0.4)	4 (1.7)	0
Hypothyroidism	94 (20.6)	2 (0.4)	1 (0.4)	0
Thyroid-stimulating hormone increased	32 (7.0)	0	3 (1.3)	0
Infection	96 (21.1)	30 (6.6)	29 (12.6)	13 (5.7)
Proteinuria	80 (17.5)	8 (1.8)	12 (5.2)	2 (0.9)
Hemorrhage	65 (14.3)	8 (1.8)	22 (9.6)	4 (1.7)

*Occurrence of any grade embolic and thrombotic events was 4.6% vs 2.2%, while gastrointestinal perforation was 3.5% vs 0.4% in patients treated with fruquintinib + BSC compared to placebo + BSC, respectively
†Includes hypertension, hypertensive crisis, increased diastolic blood pressure, increased blood pressure and hypertensive retinopathy

- The time-to-first occurrence of an AESI typically occurred within the first few cycles of treatment, with hypertension, palmar-plantar erythrodysesthesia syndrome, AST, ALT, and bilirubin increased occurring more frequently during the first 2 cycles of treatment **(Figure 3)**

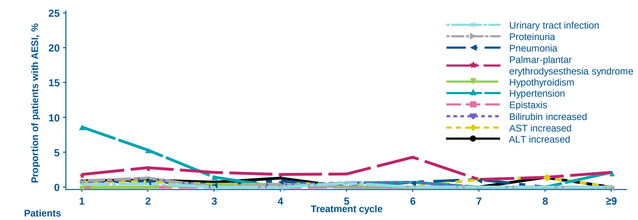
Figure 3: Time to first occurrence of treatment-emergent AESI



AESI PT (any grade), median days (Q1, Q3)	Fruquintinib + BSC (n=456)	Placebo + BSC (n=230)
Urinary tract infection	49.0 (29.0, 168.0)	63.5 (7.0, 119.5)
Proteinuria	30.0 (28.0, 84.0)	29.0 (26.5, 30.0)
Pneumonia	49.0 (20.0, 87.0)	13.0 (13.0, 13.0)
Palmar-plantar erythrodysesthesia syndrome	21.0 (12.0, 49.0)	13.0 (7.0, 24.0)
Hypothyroidism	57.0 (29.0, 104.0)	27.0 (27.0, 27.0)
Hypertension	21.0 (7.0, 48.0)	23.5 (13.0, 40.5)
Epistaxis	38.0 (14.0, 49.0)	19.0 (3.0, 21.0)
Blood bilirubin increased	56.0 (29.52, 95.5)	21.0 (21.0, 28.0)
AST increased	32.0 (21.0, 86.5)	23.0 (21.0, 29.0)
ALT increased	49.0 (28.0, 86.0)	28.0 (21.0, 28.0)

- The frequencies of AESIs over time suggest that fruquintinib + BSC has a manageable safety profile **(Summary panel and Figure 4)**

Figure 4: Occurrence of grade ≥3 treatment-emergent AESIs over time



- Grade ≥3 AESIs resulted in low rates of dose discontinuation (<1%) and dose reduction **(Table 4)**; the majority of dose reductions were to 4 mg with few patients requiring further reductions

Table 4: Selected treatment-emergent AESIs leading to dose reduction and dose discontinuation

	Patients with AESI PT leading to dose reduction				Patients with AESI PT leading to dose discontinuation			
	Fruquintinib + BSC (n=456)		Placebo + BSC (n=230)		Fruquintinib + BSC (n=456)		Placebo + BSC (n=230)	
PT, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Hypertension	17 (3.7)	15 (3.3)	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.2)	0	0
Palmar-plantar erythrodysesthesia syndrome	24 (5.3)	14 (3.1)	0	0	3 (0.7)	2 (0.4)	0	0
AST increased	1 (0.2)	0	0	0	0	0	1 (0.4)	0
ALT increased	2 (0.4)	1 (0.2)	0	0	1 (0.2)	1 (0.2)	1 (0.4)	0
Blood bilirubin increased	6 (1.3)	0	0	0	1 (0.2)	0	0	0
Proteinuria	8 (1.8)	2 (0.4)	1 (0.4)	1 (0.4)	4 (0.9)	1 (0.2)	0	0

CONCLUSIONS

- The most frequent (≥5%) any grade AESIs reported in the fruquintinib + BSC group in FRESCO-2 included hypertension, dermatological toxicity, liver function test abnormality and infections
- There were low rates of dose reduction and discontinuation due to grade ≥3 AESIs when compared with agents of the same class[5] suggesting good tolerability of fruquintinib + BSC in patients with mCRC who were heavily pretreated and had pre-existing comorbidities
- Key AESIs such as hypertension and palmar-plantar erythrodysesthesia syndrome demonstrated a predictable trend in time-to-onset, with most occurring in the first few cycles and then stabilizing at a lower rate in the later cycles. This allows for informed clinical decision making in managing these toxicities
- Overall, fruquintinib + BSC has a safety profile that is manageable, and consistent with established profile for fruquintinib monotherapy

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