Efficacy and Safety of Fruquintinib in Patients With Metastatic Colorectal Cancer According to Prior Treatment Sequence in the Refractory Setting: Results From FRESCO and FRESCO-2

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Background

- Fruquintinib, a highly selective, oral inhibitor of all three vascular endothelial growth factor receptors (VEGFRs -1, -2, and -3),[1] was approved in China in September 2018[2] and by the United States (US) Food and Drug Administration (FDA) in November 2023 as third or later line of therapy for metastatic colorectal cancer (mCRC)[3]
  - Approval in China was based on the results of the phase 3 FRESCO study (NCT02314819)[4]
  - US FDA approval was based on the results of FRESCO and the subsequent phase 3, multi-regional FRESCO-2 study (NCT04322539)[4,5]
- In FRESCO and FRESCO-2, respectively, fruquintinib plus best supportive care (BSC) demonstrated a 2.7-month and 2.6-month improvement in median overall survival (OS) versus placebo[4,5]
- The FRESCO study was conducted in China and the FRESCO-2 study was conducted in the US, Europe, Japan, and Australia; the two study populations received differing prior anti-cancer therapies per prevailing treatment guidelines[4,5]
- With multiple agents now available for the treatment of mCRC, there is a lack of data to inform optimal sequencing in the refractory setting
- The current analysis examined the efficacy and safety of fruquintinib versus placebo in patients from FRESCO and FRESCO-2 according to:
  - Whether patients had received prior trifluridine/tipiracil (TAS-102) and/or regorafenib treatment
  - The sequence in which patients had received prior TAS-102 and/or regorafenib treatment

Methods

- Both FRESCO and FRESCO-2 were phase 3, randomized, double-blind, placebo-controlled studies conducted in patients with mCRC who had progressed on prior treatment[4,5]
- In FRESCO (December 2014–May 2016), patients had received ≥2 prior chemotherapy regimens and were permitted to have received prior anti-VEGF and/or anti-EGFR therapies; TAS-102 was not widely available in China and patients previously treated with regorafenib were excluded[4]
- In FRESCO-2 (August 2020–December 2021), in addition to standard chemotherapies, anti-VEGF, and anti-EGFR therapies if indicated, prior exposure to TAS-102 and/or regorafenib was required[5]
- In both studies, eligible patients were randomized 2:1 to oral treatment with fruquintinib 5 mg or matching placebo, administered once daily on days 1–21 in 28-day cycles, plus BSC[4,5]
- The primary endpoint of both FRESCO and FRESCO-2 was OS; secondary endpoints included progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and safety[4,5]
- In the current analysis, these endpoints were assessed by the following prior treatment and sequence groups:
  - FRESCO: TAS-102 and regorafenib-naïve
  - FRESCO-2: TAS-102 only; regorafenib only; TAS-102 followed by (→) regorafenib; and regorafenib→TAS-102
- Median OS and PFS were estimated via Kaplan−Meier method, with hazard ratios (HRs) and 95% confidence intervals (CIs) estimated using Cox proportional hazards model

Results

Patients and prior treatments

- In FRESCO, 416 patients were randomized to receive fruquintinib + BSC (n=278) or placebo + BSC (n=138)
  - No patients in FRESCO had received prior regorafenib and only 16 patients (3.8%) had received prior TAS-102 (fruquintinib n=13; placebo n=3)
- In FRESCO-2, 691 patients were randomized to treatment with fruquintinib + BSC (n=461) or placebo + BSC (n=230)
  - Prior therapies in FRESCO-2 were balanced between the two treatment arms; the number of patients in each treatment sequence subgroup is shown in the study design **(Summary Panel)**
- Baseline characteristics for FRESCO and FRESCO-2 have been reported previously.[4,5] **Table 1** shows the baseline characteristics of patients according to prior TAS-102 and/or regorafenib treatment status and sequence, if applicable

Table 1: Baseline characteristics of patients in FRESCO and FRESCO-2 according to prior TAS-102 and/or regorafenib treatment status and sequence, if applicable (ITT population)

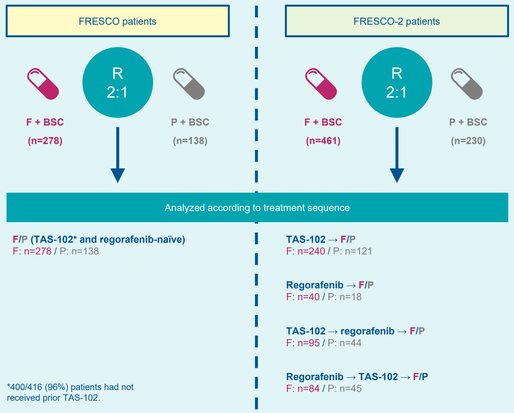
	FRESCO[4]		FRESCO-2							
	TAS-102* and regorafenib-naïve		TAS-102 only		Regorafenib only		TAS-102 → regorafenib		Regorafenib → TAS-102	
Characteristic	F (n=278)	P (n=138)	F (n=240)	P (n=121)	F (n=40)	P (n=18)	F (n=95)	P (n=44)	F (n=84)	P (n=45)
Median age, years (range)	55.0 (23–75)	57.0 (24–74)	64.0 (31–81)	63.0 (30–82)	60.0 (42–79)	60.5 (37–77)	65.0 (40–81)	64.5 (35–83)	60.0 (25–82)	66.0 (41–81)
Male, n (%)	158 (56.8)	97 (70.3)	129 (53.8)	77 (63.6)	23 (57.5)	9 (50.0)	47 (49.5)	24 (54.5)	45 (53.6)	29 (64.4)
ECOG PS of 1, n (%)	201 (72.3)	101 (73.2)	139 (57.9)	64 (52.9)	15 (37.5)	9 (50.0)	63 (66.3)	29 (65.9)	47 (56.0)	24 (53.3)
Primary site at first diagnosis: colon, n (%)†	147 (52.9)	70 (50.7)	143 (59.6)	68 (56.2)	22 (55.0)	13 (72.2)	64 (67.4)	25 (56.8)	49 (58.3)	30 (66.7)
Primary site at first diagnosis: rectum, n (%)†	125 (45.0)	60 (43.5)	75 (31.3)	38 (31.4)	14 (35.0)	4 (22.2)	26 (27.4)	14 (31.8)	27 (32.1)	13 (28.9)
Liver metastases, n (%)	185 (66.5)	102 (73.9)	177 (73.8)	77 (63.6)	30 (75.0)	13 (72.2)	69 (72.6)	36 (81.8)	62 (73.8)	29 (64.4)
Median duration of metastatic disease, (range)	16.0 (0.9–79.0)	17.2 (1.9–81.6)	35.1 (6.0–192.8)	35.8 (7.1–106.1)	28.0 (10.1–85.6)	34.4 (14.6–115.9)	40.5 (6.1–128.0)	48.8 (14.0–114.7)	48.1 (14.8–113.6)	49.4 (15.6–147.1)
≤18 months, n (%)	163 (58.6)	75 (54.3)	24 (10.0)	9 (7.4)	5 (12.5)	2 (11.1)	6 (6.3)	1 (2.3)	2 (2.4)	1 (2.2)
>18 months, n (%)	115 (41.4)	63 (45.7)	216 (90.0)	112 (92.6)	35 (87.5)	16 (88.9)	89 (93.7)	43 (97.7)	82 (97.6)	44 (97.8)
RAS mutation+, n (%)	121 (43.5)	64 (46.4)	146 (60.8)	76 (62.8)	25 (62.5)	11 (61.1)	60 (63.2)	28 (63.6)	58 (69.0)	28 (62.2)
Prior VEGF inhibitor, n (%)	84 (30.2)	41 (29.7)	228 (95.0)	119 (98.3)	39 (97.5)	14 (77.8)	92 (96.8)	43 (97.7)	84 (100.0)	43 (95.6)
Prior EGFR inhibitor, n (%)	40 (14.4)	19 (13.8)	101 (42.1)	46 (38.0)	13 (32.5)	8 (44.4)	37 (38.9)	15 (34.1)	29 (34.5)	26 (57.8)

*400 of 416 (96%) patients had not received prior TAS-102. †Remaining percentage for primary site at first diagnosis = colon and rectum. ECOG PS, Eastern Cooperative Oncology Group performance status; F, fruquintinib; ITT, intent-to-treat; P, placebo.

Question

Does prior TAS-102 and/or regorafenib treatment status and sequence affect the efficacy and safety of fruquintinib in patients with mCRC who were enrolled in FRESCO and FRESCO-2?

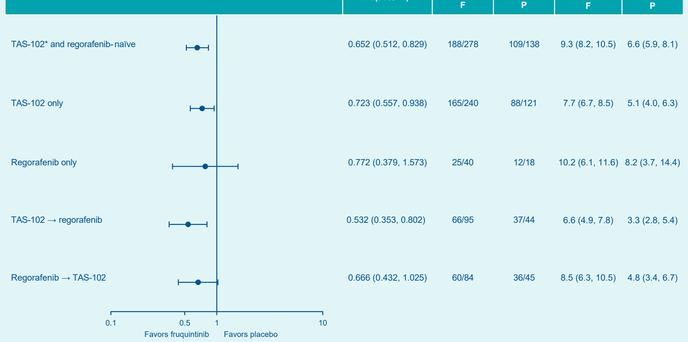
Study design



*400/416 (96%) patients had not received prior TAS-102.

Results

Figure 1: Forest plot of OS for patients in FRESCO and FRESCO-2 according to prior treatment status and sequence, if applicable (ITT population)



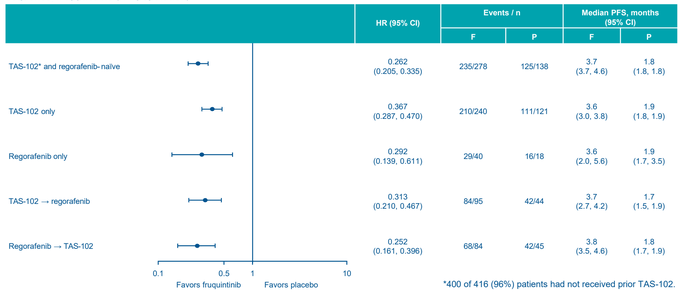
Key take aways

Fruquintinib was an effective and tolerable treatment option for patients with previously treated mCRC regardless of whether they had received prior TAS-102 or regorafenib or not. Fruquintinib was also effective and tolerable irrespective of treatment sequence. Taken together, these data provide physicians with evidence that they can use fruquintinib flexibly according to their clinical judgement in later line mCRC

Efficacy

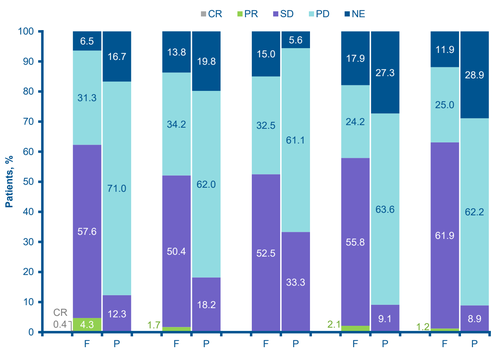
- Improvements in median OS rates were observed with fruquintinib + BSC compared with placebo + BSC and the magnitudes of survival benefit with fruquintinib were similar irrespective of prior TAS-102 and/or regorafenib treatment status and sequence, if applicable, with HRs ranging from 0.53 to 0.77 **(Figure 1, Summary Panel)**
- Comparable results were seen for PFS, with improvements in median PFS with fruquintinib versus placebo and similar magnitudes of benefit with fruquintinib regardless of prior treatment and sequence (HRs 0.25–0.37; **Figure 2**)
- The DCRs (complete response [CR] + partial response [PR] + stable disease [SD]) for patients in FRESCO who were TAS-102 and regorafenib-naïve, and patients in FRESCO-2 who had received prior TAS-102 only, regorafenib only, TAS-102→regorafenib, and regorafenib→TAS-102 were 62.2%, 52.1%, 52.5%, 57.9%, and 63.1%, respectively (**Figure 3**)

Figure 2: Forest plot of PFS for patients in FRESCO and FRESCO-2 according to prior TAS-102 and/or regorafenib treatment status and sequence, if applicable (ITT population)



*400 of 416 (96%) patients had not received prior TAS-102.

Figure 3: Tumor response according to prior TAS-102 and/or regorafenib treatment status and sequence, if applicable (ITT population*)



*Patients were response-evaluable if they had ≥1 post-baseline assessment. †400 of 416 (96%) patients had not received prior TAS-102. NE, not evaluable; PD, progressive disease.

Safety

- The treatment exposure of fruquintinib versus placebo is shown by subgroup in **Table 2**
- Rates of treatment-emergent adverse events (TEAEs), with fruquintinib + BSC were generally similar regardless of prior treatment status and sequence, if applicable **(Table 2)**
- The most common grade ≥3 TEAE with fruquintinib was hypertension regardless of whether patients did not receive prior TAS-102 or regorafenib (21.6%), or whether they received prior TAS-102 only (14.3%), regorafenib only (25.0%), TAS-102→regorafenib (11.7%), or regorafenib→TAS-102 (8.4%) **(Table 3)**
  - For patients who received prior TAS-102→regorafenib, palmar-plantar erythrodysesthesia (PPE) was reported as frequently as hypertension (11.7%) **(Table 3)**

Table 2: Treatment exposure and overall safety profile for patients in FRESCO and FRESCO-2 by prior TAS-102 and/or regorafenib treatment status and sequence, if applicable (safety population)

	FRESCO[4*]		FRESCO-2†							
	TAS-102‡/ regorafenib-naïve		TAS-102 only		Regorafenib only		TAS-102 → regorafenib		Regorafenib → TAS-102	
	F (n=278)	P (n=137)	F (n=237)	P (n=121)	F (n=40)	P (n=18)	F (n=94)	P (n=44)	F (n=83)	P (n=45)
Median duration of exposure, months (range)	3.7 (0.1–21.9)	1.8 (0.1–11.1)	2.8 (0.4–19.1)	1.8 (0.2–12.0)	3.7 (0.3–16.6)	1.8 (0.9–5.6)	2.8 (0.6–11.9)	1.8 (0.3–7.4)	3.8 (0.3–17.6)	1.8 (0.3–5.8)
Treatment cycles, n (range)	4 (1–24)	2 (1–12)	3 (1–20)	2 (1–13)	4 (1–18)	2 (1–6)	3 (1–12)	2 (1–8)	4 (1–18)	2 (1–6)
Any TEAE, n (%)	274 (98.6)	121 (88.3)	234 (98.7)	109 (90.1)	39 (97.5)	18 (100.0)	93 (98.9)	43 (97.7)	83 (100)	42 (93.3)
Grade ≥3	170 (61.2)	27 (19.7)	143 (60.3)	63 (52.1)	28 (70.0)	6 (33.3)	63 (67.0)	24 (54.5)	50 (60.2)	23 (51.1)
Treatment-related	266 (95.7)	97 (70.8)	206 (86.9)	72 (59.5)	35 (87.5)	12 (66.7)	81 (86.2)	19 (43.2)	71 (85.5)	27 (60.0)
Treatment-related grade ≥3	128 (46.0)	10 (7.3)	82 (34.6)	16 (13.2)	18 (45.0)	1 (5.6)	36 (38.3)	6 (13.6)	26 (31.3)	3 (6.7)
Leading to dose reduction	67 (24.1)	6 (4.4)	56 (23.6)	7 (5.8)	9 (22.5)	0	26 (27.7)	1 (2.3)	18 (21.7)	1 (2.2)
Leading to dose interruption	98 (35.3)	14 (10.2)	111 (46.8)	33 (27.3)	20 (50.0)	5 (27.8)	44 (46.8)	12 (27.3)	36 (43.4)	11 (24.4)
Leading to treatment discontinuation	42 (15.1)	8 (5.8)	53 (22.4)	22 (18.2)	5 (12.5)	5 (27.8)	19 (20.2)	13 (29.5)	15 (18.1)	9 (20.0)

*1 patient assigned to placebo did not receive treatment. †Of 5 patients assigned to fruquintinib, 3 did not receive fruquintinib, and 2 patients received placebo instead; 2 patients assigned to placebo did not receive treatment. ‡400 of 416 (96%) patients had not received prior TAS-102.

Table 3: Grade ≥3 TEAEs occurring in ≥5% of patients in the fruquintinib arm of any subgroup (safety population)

	FRESCO[4*]		FRESCO-2†							
	TAS-102‡/ regorafenib-naïve		TAS-102 only		Regorafenib only		TAS-102 → regorafenib		Regorafenib → TAS-102	
Patients, n (%)	F (n=278)	P (n=137)	F (n=237)	P (n=121)	F (n=40)	P (n=18)	F (n=94)	P (n=44)	F (n=83)	P (n=45)
Hypertension	60 (21.6)	3 (2.2)	34 (14.3)	2 (1.7)	10 (25.0)	0	11 (11.7)	0	7 (8.4)	0
PPE	30 (10.8)	0	4 (1.7)	0	7 (17.5)	0	11 (11.7)	0	6 (7.2)	0
Diarrhea	9 (3.2)	0	6 (2.5)	0	0	0	7 (7.4)	0	3 (3.6)	0
Fatigue	5 (1.8)	2 (1.5)	7 (3.0)	1 (0.8)	1 (2.5)	0	8 (8.5)	0	2 (2.4)	1 (2.2)
Asthenia	2 (0.7)	0	25 (10.5)	4 (3.3)	1 (2.5)	1 (5.6)	4 (4.3)	3 (6.8)	5 (6.0)	1 (2.2)
Stomatitis	1 (0.4)	0	3 (1.3)	1 (0.8)	3 (7.5)	0	1 (1.1)	0	1 (1.2)	0
Disease progression	N/A§	N/A§	13 (5.5)	16 (13.2)	4 (10.0)	0	5 (5.3)	5 (11.4)	5 (6.0)	7 (15.6)
General physical health deterioration	N/A§	N/A§	3 (1.3)	4 (3.3)	0	0	7 (7.4)	1 (2.3)	1 (1.2)	0

*1 patient assigned to placebo did not receive treatment. †Of 5 patients assigned to fruquintinib, 3 did not receive fruquintinib, and 2 patients received placebo instead; 2 patients assigned to placebo did not receive treatment. ‡400 of 416 (96%) patients had not received prior TAS-102. §Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 25.0) and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 in FRESCO and version 5.0 in FRESCO-2; disease progression grading was not included in version 4.03; general physical health deterioration was graded by the FRESCO-2 study investigator.

Conclusions

- Fruquintinib + BSC was associated with an improvement in both OS and PFS compared with placebo in patients who had not received TAS-102 or regorafenib and in patients who had previously received TAS-102 and/or regorafenib, irrespective of treatment sequence
- The overall rate of TEAEs with fruquintinib was consistent regardless of prior TAS-102 and/or regorafenib treatment status or sequence, if applicable, and no new safety signals were observed within the subgroup data
- Fruquintinib was an effective and tolerable treatment option for patients with previously treated mCRC regardless of whether they had received prior TAS-102 or regorafenib or not. Fruquintinib was also effective and tolerable irrespective of treatment sequence. Taken together, these data provide physicians with evidence that they can use fruquintinib flexibly according to their clinical judgement in later line mCRC

References

1. Sun Q, et al. *Cancer Biol Ther*. 2014;15:1635−45
2. Shirley M. *Drugs*, 2018;78:1757−61
3. FRUZAQLA™ (fruquintinib) Prescribing Information. Published Nov 2023. Takeda Pharmaceuticals America, Inc., Lexington, MA, USA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/217564s000lbl.pdf. Accessed Feb 2024
4. Li J, et al. *JAMA*. 2018;319:2486−96
5. Dasari A, et al. *Lancet*. 2023;402:41−53

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