Subgroup Analysis of Patients With Metastatic Colorectal Cancer Treated With Fruquintinib in the FRESCO Trial Who Had Liver Metastasis

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Disclosure

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Background and Objective

- CRC is the fourth leading cause of cancer mortality in the world[1] and is the second most common cancer type in China[2]
- The development of metastases is the main cause of death in patients with CRC; about 70% of patients with CRC develop liver metastases during the course of their disease[3,4]
- Fruquintinib is a highly selective and potent small molecule oral inhibitor of VEGF receptors 1, 2, and 3[5]
  - In the phase 3 FRESCO trial, fruquintinib demonstrated a statistically significant and clinically meaningful OS benefit in third-line mCRC patients in China, and the safety profile was consistent with that of its class[6]
- The aim of the present subgroup analysis is to determine the benefit of fruquintinib in mCRC patients associated with liver metastasis who were receiving third-line or posterior-line treatment

Abbreviations: CRC=colorectal cancer; mCRC=metastatic colorectal cancer; OS=overall survival; VEGF=vascular endothelial growth factor

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Figure 1. Study Design (FRESCO Trial[1])

mCRC progressed after 2 or more lines of chemotherapy
Patients screened=519
Randomized=416

→ R (2:1)

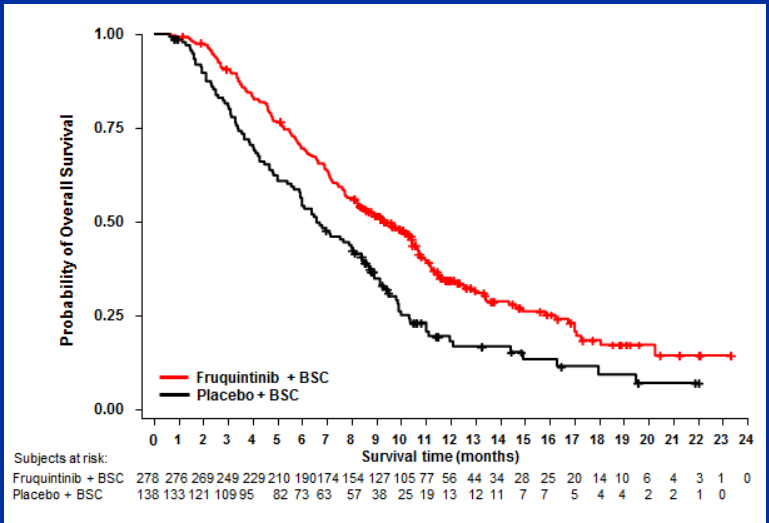
→ Fruquintinib+BSC 5 mg QD 3 weeks on/1 week off (4-week cycle) N=278

→ Placebo+BSC N=138

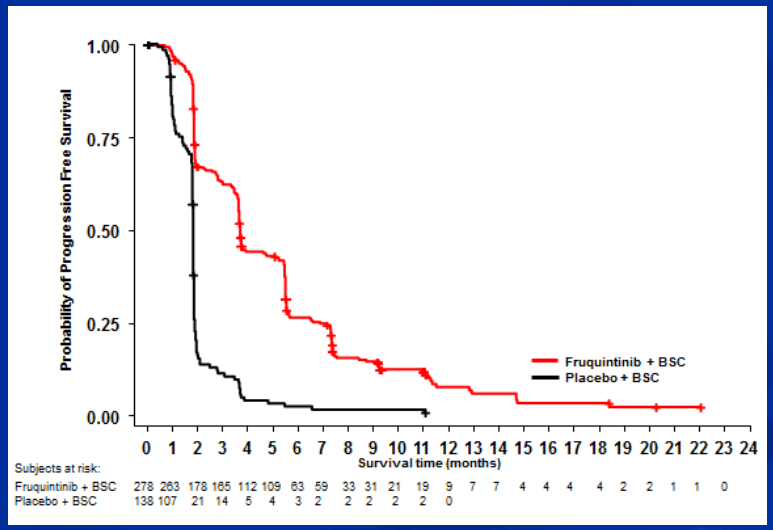
→ Continue treatment until PD, intolerable toxicity, or withdrawal

Tumor response assessment every 8 weeks per RECIST v1.1

Overall Survival



Progression-Free Survival



Abbreviations: BSC=best supportive care; mCRC=metastatic colorectal cancer; PD=progressive disease; QD=once daily; R=randomization; RECIST=Response Evaluation Criteria In Solid Tumors

[1]Li J, et al. *JAMA*. 2018;319(24):2486-96.

Methods

Key Inclusion Criteria

- Histologically and/or cytologically diagnosed with mCRC (Stage IV)
- Had tumor progression after treatment regimens with fluropyrimidine, oxaliplatin, and irinotecan
- Prior anti-VEGF- or anti-EGFR-targeted therapy allowed but not mandatory
- Aged 18-75 years, ECOG performance status 0-1, life expectancy ≥3 months
- Measurable disease according to RECIST v1.1
- Adequate bone marrow, liver, and renal function

Abbreviations: ECOG=Eastern Cooperative Oncology Group; EGFR=anti-epidermal growth factor receptor; mCRC=metastatic colorectal cancer; RECIST=Response Evaluation Criteria In Solid Tumors; VEGF=vascular endothelial growth factor

Subgroup Analysis Endpoints

- **Efficacy:**
  - Overall survival
  - Progression-free survival
  - Tumor response (ORR/DCR)
- **Safety:**
  - Treatment-emergent hepatotoxicity (by CTCAE grades and laboratory abnormalities)

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; DCR=disease control rate; ORR=overall response rate

Statistical Analyses

- OS and PFS evaluated by Kaplan-Meier method
- Hazard ratio estimated through Cox proportional hazards model; p-value generated from log-rank test
- ORR and DCR compared using Cochran-Mantel-Haenszel test
- Hepatic AEs evaluated by the standardized MedDRA queries of hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions
  - According to whether patient had liver metastasis at baseline and AEs were categorized by CTCAE grades

Abbreviations: AEs=adverse events; CTCAE=Common Terminology Criteria for Adverse Events; DCR=disease control rate; MedDRA=Medical Dictionary for Regulatory Activities; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

Results

Table 1. Demographic and Baseline Disease Characteristics

Variables	Patients With Liver Metastasis		Patients Without Liver Metastasis	
	Fruquintinib+BSC (N=185)	Placebo+BSC (N=102)	Fruquintinib+BSC (N=93)	Placebo+BSC (N=36)
Age group, n (%)				
<65 years	148 (80.0)	83 (81.4)	80 (86.0)	27 (75.0)
≥65 years	37 (20.0)	19 (18.6)	13 (14.0)	9 (25.0)
Gender, n (%)				
Male/female	109 (58.9)/76 (41.1)	74 (72.5)/28 (27.5)	49 (52.7)/44 (47.3)	23 (63.9)/13 (36.1)
ECOG performance status, n (%)				
0	53 (28.6)	31 (30.4)	24 (25.8)	6 (16.7)
1	132 (71.4)	71 (69.6)	69 (74.2)	30 (83.3)
Primary site at the time of diagnosis, n (%)				
Left*	137 (74.1)	85 (83.3)	77 (82.8)	30 (83.3)
Right**	42 (22.7)	15 (14.7)	14 (15.1)	6 (16.7)
Both left and right	4 (2.2)	0	0	0
Metastatic site, n (%)				
Single	7 (3.8)	3 (2.9)	6 (6.5)	1 (2.8)
Multiple	178 (96.2)	99 (97.1)	87 (93.5)	35 (97.2)
Stage of disease at the time of diagnosis, n (%)				
I	4 (2.2)	4 (3.9)	4 (4.3)	0
II	22 (11.9)	8 (7.8)	12 (12.9)	10 (27.8)
III	65 (35.1)	35 (34.3)	53 (57.0)	16 (44.4)
IV	93 (50.3)	53 (52.0)	24 (25.8)	10 (27.8)
Time from first metastasis diagnosis to randomization (months)				
Mean (SD)	18.15 (12.2)	18.18 (11.9)	20.46 (14.3)	27.34 (19.2)
Median (min, max)	15.18 (2.1, 61.6)	14.74 (1.9, 63.6)	17.68 (0.9, 79.0)	23.03 (4.0, 81.6)
Prior use of VEGF inhibitors, n (%)				
Yes	53 (28.6)	27 (26.5)	31 (33.3)	13 (36.1)
Prior use of EGFR inhibitors, n (%)				
Yes	32 (17.3)	16 (15.7)	8 (8.6)	3 (8.3)
K-RAS gene status, n (%)				
Wild type	111 (60.0)	57 (55.9)	46 (49.5)	17 (47.2)
Mutant type	74 (40.0)	45 (44.1)	47 (50.5)	19 (52.8)
Prior treatment lines on or above metastatic disease, n (%)				
≤3	149 (80.5)	80 (78.4)	72 (77.4)	27 (75.0)
>3	36 (19.5)	22 (21.6)	21 (22.6)	9 (25.0)

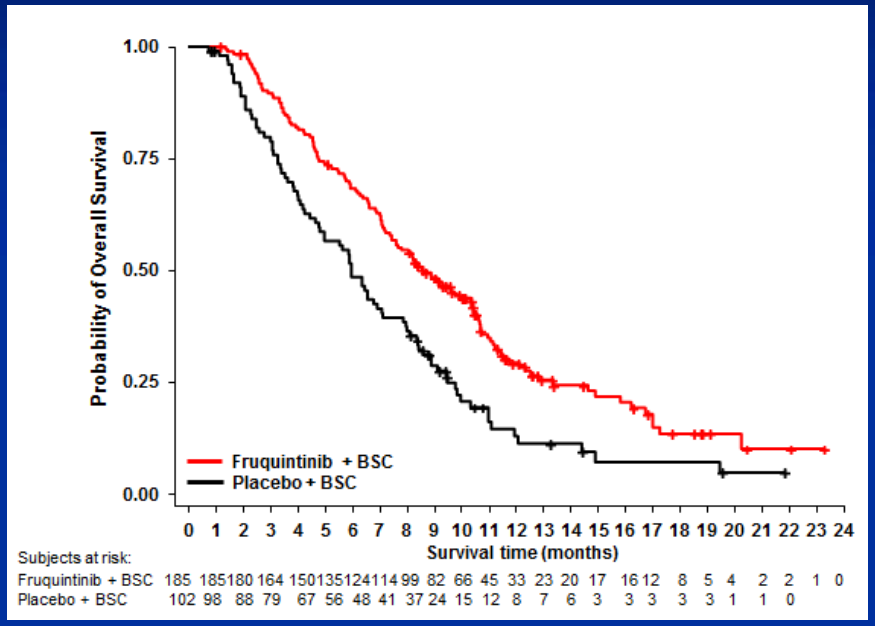
* Left region includes splenic flexure, descending, transverse, and sigmoid colon, and rectum

** Right region includes cecum, ascending colon, and hepatic flexure

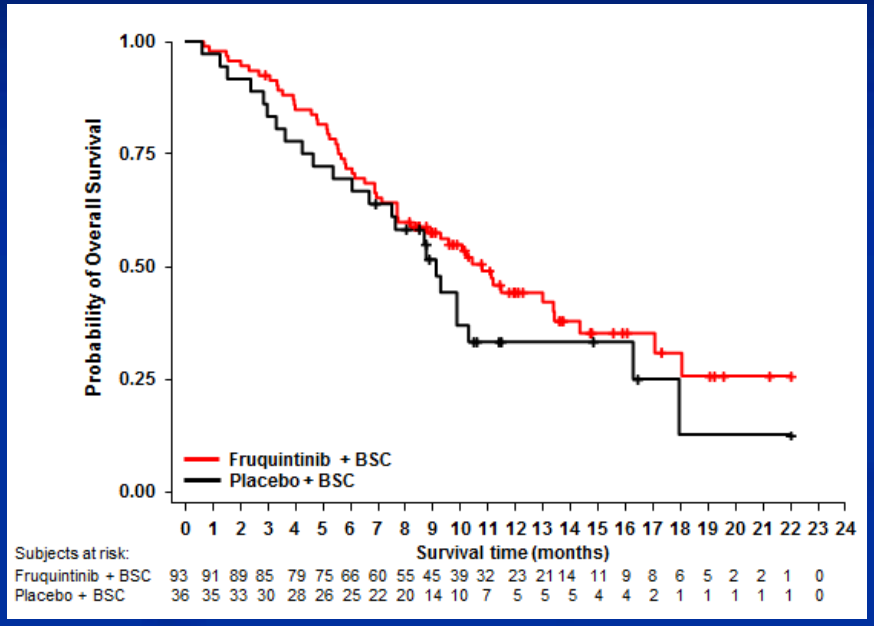
Abbreviations: BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; EGFR=anti-epidermal growth factor receptor; max=maximum; min=minimum; SD=standard deviation; VEGF=vascular endothelial growth factor

Figure 2. Overall Survival in Patients With or Without Liver Metastasis (ITT Population)

Patients With Liver Metastasis



Patients Without Liver Metastasis



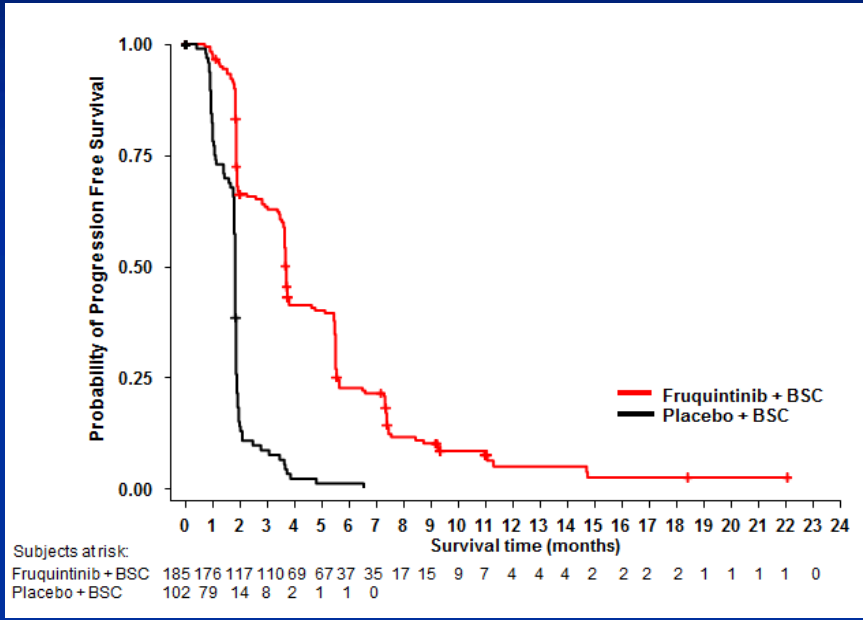
	Fruquintinib + BSC (N=185)	Placebo + BSC (N=102)	Fruquintinib + BSC (N=93)	Placebo + BSC (N=36)
Median, months (95% CI)	8.61 (7.46, 10.38)	5.98 (4.80, 7.13)	10.81 (7.75, 13.44)	9.13 (6.70, 10.32)
HR (95% CI)	0.59 (0.45, 0.77)		0.75 (0.46, 1.21)	
p-value	<.001		.240	

p-value is based on log-rank test

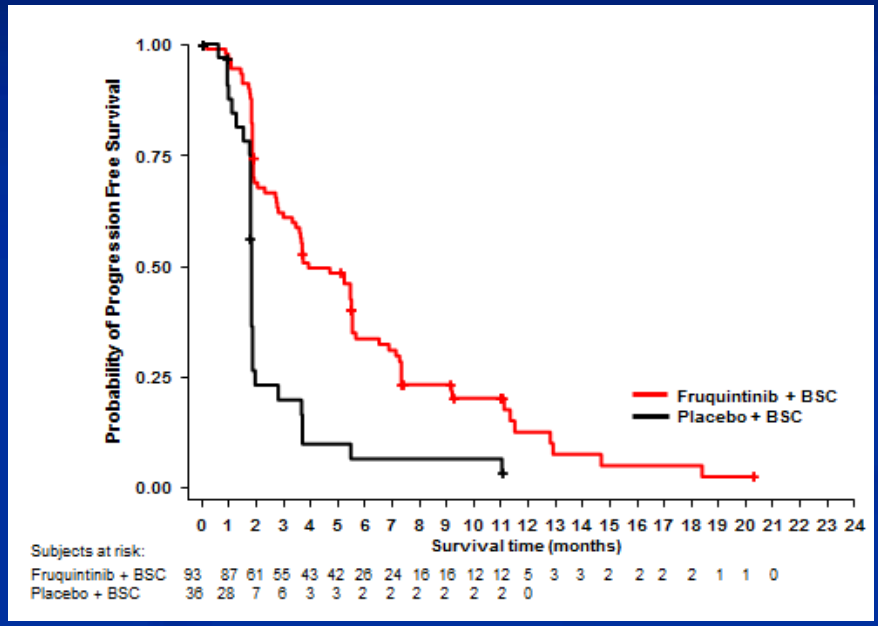
Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat

Figure 3. Progression-Free Survival in Patients With or Without Liver Metastasis (ITT Population)

Patients With Liver Metastasis



Patients Without Liver Metastasis



	Fruquintinib + BSC (N=185)	Placebo + BSC (N=102)	Fruquintinib + BSC (N=93)	Placebo + BSC (N=36)
Median, months (95% CI)	3.71 (3.65, 3.81)	1.84 (1.81, 1.84)	3.94 (3.35, 5.55)	1.84 (1.81, 1.87)
HR (95% CI)	0.22 (0.17, 0.30)		0.34 (0.22, 0.53)	
p-value	<.001		<.001	

p-value is based on log-rank test

Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; ITT=intent-to-treat

Table 2. Overall Survival Subgroups

Liver Metastasis Subgroup	Fruquintinib (Events/N)	Placebo (Events/N)	Median Survival, months (95% CI)		p-value	HR (95% CI)
			Fruquintinib	Placebo		
Lung metastasis						
Yes	78/104	52/62	8.57 (7.10, 9.95)	4.83 (3.88, 6.57)	.002	0.57 (0.40, 0.82)
No	56/81	33/40	9.76 (7.10, 10.71)	7.56 (5.55, 8.90)	.034	0.63 (0.41, 0.97)
Prior targeted therapy						
Anti-VEGF or anti-EGFR	58/77	33/40	7.46 (6.87, 9.95)	5.65 (4.01, 8.38)	.012	0.57 (0.37, 0.89)
No anti-VEGF and no anti-EGFR	76/108	52/62	9.23 (7.82, 10.71)	6.47 (4.67, 8.02)	.005	0.60 (0.42, 0.86)
K-RAS status						
Wild type	78/111	45/57	10.38 (7.69,10.97)	5.98 (4.47, 7.98)	.001	0.55 (0.38, 0.79)
Mutated	56/74	40/45	7.46 (5.78, 8.90)	6.37 (3.88, 8.02)	.085	0.70 (0.46, 1.05)

HR and 95% CI are from unstratified Cox model and p-value is from unstratified log rank test

Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; N=number of planned patients; VEGF=vascular endothelial growth factor

Table 3. Response Rate

	Patients With Liver Metastasis		Patients Without Liver Metastasis	
	Fruquintinib + BSC (N=185)	Placebo+ BSC (N=102)	Fruquintinib + BSC (N=93)	Placebo + BSC (N=36)
Best overall response, n (%)				
Complete response	0	0	1 (1.1)	0
Partial response	9 (4.9)	0	3 (3.2)	0
Stable disease	106 (57.3)	9 (8.8)	54 (58.1)	8 (22.2)
Progressive disease	59 (31.9)	77 (75.5)	28 (30.1)	21 (58.3)
Not assessable	11 (5.9)	16 (15.7)	7 (7.5)	7 (19.4)
ORR, n (%)	9 (4.9)*	0	4 (4.3)	0
DCR, n (%)	115 (62.2)**	9 (8.8)	58 (62.4)**	8 (22.2)
Median DOS, months (95% CI)	5.5 (4.8, 5.5)	3.7 (3.1, 4.8)	5.7 (5.5, 7.4)	3.7 (2.8, 11.0)

*p<.05, **p<.001, p-value (fruquintinib vs. placebo) based on Cochran–Mantel–Haenszel test

Abbreviations: BSC=best supportive care; CI=confidence interval; DCR=disease control rate; DOS=duration of stable disease; N=number of planned patients; n=number of patients; ORR=overall response rate

Table 4. Treatment-Emergent Hepatotoxicity (Safety Population)

Grade	Patients With Liver Metastasis		Patients Without Liver Metastasis	
	Fruquintinib + BSC (N=185) n (%)	Placebo + BSC (N=102) n (%)	Fruquintinib + BSC (N=93) n (%)	Placebo + BSC (N=35) n (%)
Any Grade	7 (3.8)	2 (2.0)	2 (2.2)	0
Grade 1	5 (2.7)	1 (1.0)	0	0
Grade 2	2 (1.1)	0	1 (1.1)	0
Grade 3	0	1 (1.0)	1 (1.1)	0
Grade 4	0	0	0	0
Grade 5	0	0	0	0

Abbreviations: BSC=best supportive care

Table 5. Treatment-Emergent Hepatic Laboratory Abnormalities (Safety Population)

Characteristics	Patients With Liver Metastasis		Patients Without Liver Metastasis	
	Fruquintinib + BSC (N=185) n (%)	Placebo + BSC (N=102) n (%)	Fruquintinib + BSC (N=93) n (%)	Placebo + BSC (N=35) n (%)
AST/ALT >3x ULN and ≤5x ULN	18 (9.7)	5 (4.9)	1 (1.1)	1 (2.9)
AST/ALT >5x ULN	10 (5.4)	3 (2.9)	2 (2.2)	0
Total bilirubin >2x ULN	30 (16.2)	10 (9.8)	1 (1.1)	1 (2.9)
AST/ALT >3x ULN and total bilirubin >2x ULN	14 (7.6)	1 (1.0)	0	1 (2.9)
Hy's law laboratory criteria*	1 (0.5)	0	0	0

*AST/ALT >3x ULN, total bilirubin >2x ULN and ALP <2x ULN.
Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; ULN=upper limit of normal.

Summary of Results

- **Efficacy:**
  - In patients with liver metastasis, treatment with fruquintinib demonstrated a significant survival improvement as compared to placebo
    - Median OS: 8.61 vs. 5.98 months (HR=0.59, 95% CI: 0.45-0.77, p<.001)
    - Median PFS: 3.71 vs.1.84 months (HR=0.22, 95% CI: 0.17-0.30, p<.001)
  - Fruquintinib conferred improvements over placebo in patients with liver metastasis for ORR (4.9% vs. 0%, p=029), DCR (62.2% vs. 8.8%, p<.001), and OS in liver metastasis subgroups
- **Safety:**
  - In patients with liver metastasis, treatment-emergent hepatic toxicities of any grade occurred in 7 (3.8%) patients in the fruquintinib group versus 2 (2.0%) in the placebo group

Abbreviations: CI=confidence interval; DCR=disease control rate; HR=hazard ratio; ORR=overall response rate; OS=overall survival; PFS=progression-free survival

Conclusions

- In this subgroup analysis, fruquintinib demonstrated a statistically significant increase in OS and PFS as compared with placebo in CRC patients with liver metastasis.
- The hepatotoxicity of fruquintinib was comparable with placebo in CRC patients with liver metastasis.

Abbreviations: CRC=colorectal cancer; OS=overall survival; PFS=progression-free survival

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