3537

Subgroup Analysis by Prior Anti-VEGF or Anti-EGFR Target Therapy in FRESCO, A Randomized, Double-Blind, Phase III Trial Comparing Fruquintinib Versus Placebo Plus Best Supportive Care in Chinese Patients With Metastatic Colorectal Cancer (mCRC)

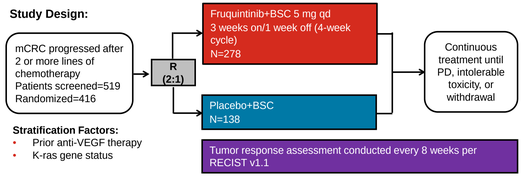
Ruihua Xu[1], Jin Li[2,3], Yuxian Bai[4], Yanhong Deng[5], Lei Yang[6], Haijun Zhong[7], Zhendong Chen[8], Hongming Pan[9], Weijian Guo[3], Yongqian Shu[10], Ying Yuan[11], Jianming Xu[12], Lin Shen[13], Ning Wang[14], Xin Wang[14], Hai Dong Chi[14], Mengye Peng[15], Ye Hua[15], Weiguo Su[15], Shukui Qin[16]

[1]Sun Yat-Sen University Cancer Center, Guangzhou, China; [2]Tongji University Shanghai East Hospital, Shanghai, China; [3]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China; [4]Harbin Medical University Cancer Hospital, Department of Medical Oncology, Harbin, China; [5]Sun Yat-sen University, Guangzhou, China; [6]Nantong Tumor Hospital, Nantong, China; [7]Zhejiang Cancer Hospital, Hangzhou, China; [8]2nd Hospital of Anhui Medical University, Hefei, China; [9]Sir Run Run Shaw Hospital, Medical College of Zhejiang University, Hangzhou, China; [10]Jiangsu Provincial Hospital, Department of medical oncology, Nanjing, China; [11]Second Hospital of Zhejiang University, Hangzhou, China; [12]307th hospital of Chinese PLA- the affiliated hospital of Military Medical Sciences, Department of medical oncology, Beijing, China; [13]Key Laboratory of Carcinogenesis and Translational Research, Ministry of Education, Beijing, Department of Gastrointestinal Oncology, Peking University Cancer Hospital and Institute, Beijing, China; [14]Eli Lilly and Company, Shanghai, China; [15]Hutchison MediPharma Limited, Shanghai, China; [16]PLA 81 Hospital, Department of Medical Oncology, Nanjing, China

BACKGROUND

- Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer mortality in the world[1-3]; in China, 376,000 new cases of CRC per year have been reported in 2015 and growing[4]; approximately 50% of the cases develop into metastatic or advanced CRC (mCRC)[5,6]
- Patients with mCRC are typically offered chemotherapy (fluoropyrimidines plus either oxaliplatin or irinotecan) and might also receive prior target therapy drugs targeting vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) or both as first- or second-line systemic therapy
- Fruquintinib is a next-generation, highly selective, and potent oral inhibitor of VEGF receptor 1, 2, and 3[7]; in the Phase III FRESCO trial, fruquintinib demonstrated a statistically significant and clinically meaningful overall survival (OS) benefit in Chinese patients with mCRC; fruquintinib was well tolerated, and the safety profile was consistent with that of its class[8]
- The objective of the present analysis was to explore possible effects of prior target therapy on the efficacy and safety of fruquintinib; thus, we conducted subgroup analysis of patients with prior target therapy (PTT) and those without prior target therapy (non-PTT) in the FRESCO trial

Figure 1. FRESCO Trial (NCT02314819) Study Design



Results:

Overall Survival

	Fruquintinib+BSC (N=278)	Placebo+BSC (N=138)
Median (months)	9.30	6.57
95% CI	8.18-10.45	5.88-8.11
Stratified HR (95% CI)	0.65 (0.51-0.83)	
p-value	<0.001	

Progression-Free Survival

	Fruquintinib+BSC (N=278)	Placebo+BSC (N=138)
Median (months)	3.71	1.84
95% CI	3.65-4.63	1.81-1.84
Stratified HR (95% CI)	0.26 (0.21-0.34)	
p-value	<0.001	

Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; mCRC=metastatic colorectal cancer; N=number of planned patients; PD=progressive disease; q3=once per day; RECIST=Response Evaluation Criteria In Solid Tumors

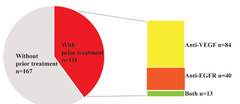
METHODS

- Overall survival (OS) and progression-free survival (PFS) were evaluated by Kaplan-Meier method; hazard ratio (HR) was estimated through Cox proportional hazards model; p-value was generated from log rank test
- Prior used anti-VEGF drugs included bevacizumab and aflibercept; prior used anti-EGFR drugs included cetuximab, nimotuzumab and panitumumab

RESULTS

Proportion of Fruquintinib-Treated Patients With and Without Prior Target Treatment in FRESCO

- Among a total of 278 fruquintinib-treated patients, 111 received prior target therapy (84 with anti-VEGF, 40 with anti-EGFR, and 13 with both), whereas 167 (60.1%) did not receive any prior target therapy
- Prior anti-VEGF in Fruquintinib vs placebo: 30.2% vs 29.7%, respectively; prior anti-EGFR: 14.4% vs 13.8%, respectively



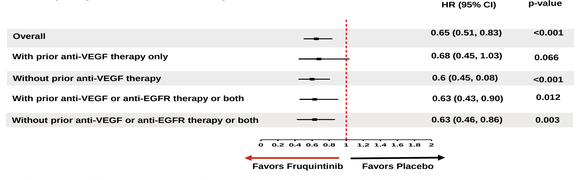
Abbreviations: VEGF=Vascular endothelial growth factor; EGFR=Epidermal growth factor receptor; n=number of planned patients

Table 1. Demographic and Baseline Characteristics by Prior Therapy in FRESCO

Variables	Without Prior Anti-VEGF/Anti-EGFR Therapy		With Prior Anti-VEGF/Anti-EGFR Therapy	
	Fruquintinib+BSC (N=167)	Placebo+BSC (N=83)	Fruquintinib+BSC (N=111)	Placebo+BSC (N=55)
Age, n (%)				
<65 years	132 (79.0)	67 (80.7)	96 (86.5)	43 (78.2)
≥65 years	35 (21.0)	16 (19.3)	15 (13.5)	12 (21.8)
Gender, n (%)				
Male/female	101 (60.5)/66 (39.5)	57 (68.7)/26 (31.3)	57 (51.4)/54 (48.6)	40 (72.7)/15 (27.3)
ECOG performance status, n (%)				
0	46 (27.5)	23 (27.7)	31 (27.9)	14 (25.5)
1	121 (72.5)	60 (72.3)	80 (72.1)	41 (74.5)
Primary site at the time of diagnosis				
Left*	128 (76.6)	70 (84.3)	86 (77.5)	45 (81.8)
Right**	34 (20.4)	11 (13.3)	22 (19.8)	10 (18.2)
Both left and right	3 (1.8)	0	1 (0.9)	0
Metastatic site				
Single	9 (5.4)	2 (2.4)	4 (3.6)	2 (3.6)
Multiple	158 (94.6)	81 (97.6)	107 (96.4)	53 (96.4)
Liver metastasis				
Yes	108 (64.7)	62 (74.7)	77 (69.4)	40 (72.7)
No	59 (35.3)	21 (25.3)	34 (30.6)	15 (27.3)
Time from first metastasis diagnosis to randomization (months)				
Mean (SD)	15.8 (11.00)	16.3 (10.97)	23.7 (14.20)	27.0 (17.04)
Median (min, max)	13.4 (0.9, 66.3)	13.8 (1.9, 68.5)	21.4 (2.2, 79.0)	22.9 (4.2, 81.6)
Length by categorical				
<18 Months	116 (69.5)	55 (66.3)	47 (42.3)	20 (36.4)
>=18 Months	51 (30.5)	28 (33.7)	64 (57.7)	35 (63.6)
K-ras gene status				
Wild type	88 (52.7)	43 (51.8)	69 (62.2)	31 (56.4)
Mutant type	79 (47.3)	40 (48.2)	42 (37.8)	24 (43.6)
Prior treatment lines on or above metastatic disease				
<=3	143 (85.6)	74 (89.2)	78 (70.3)	33 (60.0)
>3	24 (14.4)	9 (10.8)	33 (29.7)	22 (40.0)

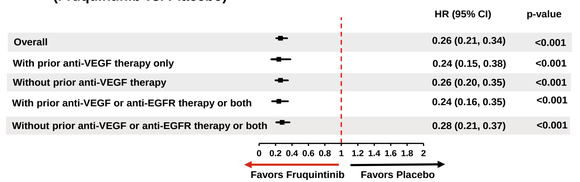
*Abbreviations: BMI=body mass index; BSC=best supportive care; ECOG=Eastern Cooperative Oncology Group; EGFR=epidermal growth factor receptor; N=number of planned patients; n=number of patients; SD=standard deviation; VEGF=vascular endothelial growth factor; *includes splenic flexure, descending colon, transverse colon, sigmoid colon, and rectum; **includes cecum, ascending colon, and hepatic flexure*

Figure 2. Overall Survival Subgroup Analysis by Prior Treatment: Forest Plot (Fruquintinib vs. Placebo)



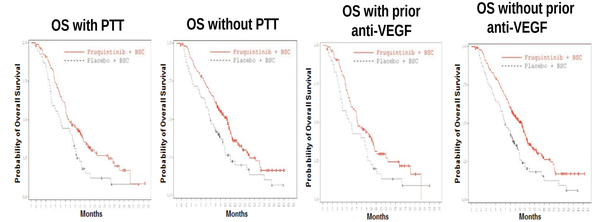
Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; VEGF=vascular endothelial growth factor

Figure 3. Progression-Free Survival Subgroup Analysis by Prior Treatment: Forest Plot (Fruquintinib vs. Placebo)



Abbreviations: CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; VEGF=vascular endothelial growth factor

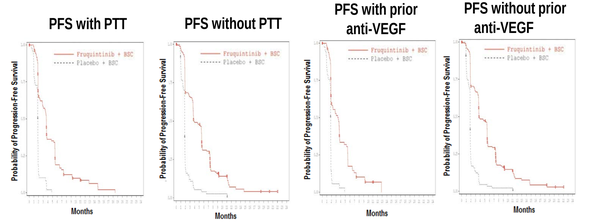
Figure 4. Overall Survival by Prior Therapy of All Randomized Patients



	Fruquintinib+BSC (N=111)	PBO+BSC (N=55)	Fruquintinib+BSC (N=167)	PBO+BSC (N=83)	Fruquintinib+BSC (N=84)	PBO+BSC (N=41)	Fruquintinib+BSC (N=194)	PBO+BSC (N=97)
Median, months (95% CI)	7.69 (6.90, 10.09)	5.98 (4.21, 8.41)	10.35 (8.57, 11.07)	6.93 (5.91, 8.77)	7.20 (5.85, 10.09)	5.91 (3.88, 8.71)	10.35 (8.44, 11.07)	6.93 (5.98, 8.41)
HR (95% CI)	0.63 (0.43, 0.90)		0.63 (0.46, 0.86)		0.68 (0.45, 1.03)		0.60 (0.45, 0.80)	
p-value (log rank)	0.012		0.003		0.066		<0.001	

Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; n=number of patients; OS= overall survival; PBO=placebo; PTT=prior target therapy (prior anti-VEGF or anti-EGFR or both)

Figure 5. Progression-Free Survival by Prior Therapy of All Randomized Patients



	Fruquintinib+ BSC (N=111)	PBO+BSC (N=55)	Fruquintinib+BSC (N=167)	PBO+BSC (N=83)	Fruquintinib+BSC (N=84)	PBO+BSC (N=41)	Fruquintinib+BSC (N=194)	PBO+BSC (N=97)
Median, months (95% CI)	3.65 (2.83, 3.71)	1.84 (1.81, 1.84)	3.81 (3.68, 5.49)	1.84 (1.84, 1.87)	3.48 (1.94, 3.71)	1.84 (1.81, 1.84)	3.81 (3.68, 5.49)	1.84 (1.81, 1.87)
HR (95% CI)	0.24 (0.16, 0.35)		0.28 (0.21, 0.37)		0.24 (0.15, 0.38)		0.26 (0.20, 0.35)	
p-value (log rank)	<0.001		<0.001		<0.001		<0.001	

Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; n=number of patients; PFS=progression-free survival; PBO=placebo; PTT=prior target therapy (prior anti-VEGF or anti-EGFR or both)

Table 2. Summary of Related Treatment-Emergent Adverse Events (Any Grade ≥20% of Patients) by Prior Anti-VEGF/Anti-EGFR Therapy in FRESCO

	Without Prior Anti-VEGF/Anti-EGFR Therapy						With Prior Anti-VEGF/Anti-EGFR Therapy					
	Fruquintinib+BSC (N=167), n (%)			Placebo+BSC (N=82), n (%)			Fruquintinib+BSC (N=111), n (%)			Placebo+BSC (N=55), n (%)		
Preferred Term	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5
Subjects with any related TEAE	158 (94.6)	74 (44.3)	1 (0.6)	55 (67.1)	4 (4.9)	0	108 (97.3)	50 (45.0)	3 (2.7)	42 (76.4)	6 (10.9)	0
Hypertension	93 (55.7)	36 (21.6)	0	12 (14.6)	0	0	61 (55.0)	23 (20.7)	0	9 (16.4)	3 (5.5)	0
Hand-foot-skin reaction	92 (55.1)	22 (13.2)	0	3 (3.7)	0	0	45 (40.5)	8 (7.2)	0	1 (1.8)	0	0
Proteinuria	59 (35.3)	3 (1.8)	0	22 (26.8)	0	0	58 (52.3)	6 (5.4)	0	12 (21.8)	0	0
Dysphonia	59 (35.3)	0	0	2 (2.4)	0	0	41 (36.9)	0	0	0	0	0
AST increased	34 (20.4)	0	0	7 (8.5)	0	0	30 (27.0)	1 (0.9)	0	7 (12.7)	1 (1.8)	0
TSH increased	42 (25.1)	0	0	1 (1.2)	0	0	27 (24.3)	0	0	2 (3.6)	0	0
Blood bilirubin increased	33 (19.8)	3 (1.8)	0	6 (7.3)	2 (2.4)	0	23 (20.7)	1 (0.9)	0	4 (7.3)	0	0
ALT increased	25 (15.0)	1 (0.6)	0	7 (8.5)	0	0	25 (22.5)	1 (0.9)	0	5 (9.1)	2 (3.6)	0
Diarrhea	25 (15.0)	3 (1.8)	0	2 (2.4)	0	0	31 (27.9)	5 (4.5)	0	1 (1.8)	0	0
Stomatitis	34 (20.4)	0	0	0	0	0	13 (11.7)	1 (0.9)	0	0	0	0

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BSC=best supportive care; EGFR=epidermal growth factor receptor; N=number of planned patients; n=number of patients; TEAE=treatment-emergent adverse event; TSH=thyroid-stimulating hormone; VEGF=vascular endothelial growth factor

Table 3. Summary of Related Treatment-Emergent Adverse Events (Any Grade ≥20% of Patients) by Prior Anti-VEGF Therapy in FRESCO

	Without Prior VEGF Therapy						With Prior VEGF Therapy					
	Fruquintinib+BSC (N=194), n (%)			Placebo+BSC (N=96), n (%)			Fruquintinib+BSC (N=84), n (%)			Placebo+BSC (N=41), n (%)		
Preferred Term	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5	All Grades	Grades 3-4	Grade 5
Subjects with any related TEAE	185 (95.4)	83 (42.8)	1 (0.5)	64 (66.7)	4 (4.2)	0	81 (96.4)	41 (48.8)	3 (3.6)	33 (80.5)	6 (14.6)	0
Hypertension	106 (54.6)	39 (20.1)	0	15 (15.6)	0	0	48 (57.1)	20 (23.8)	0	6 (14.6)	3 (7.3)	0
Hand-foot-skin reaction	106 (54.6)	24 (12.4)	0	4 (4.2)	0	0	31 (36.9)	6 (7.1)	0	0	0	0
Proteinuria	68 (35.1)	3 (1.5)	0	24 (25.0)	0	0	49 (58.3)	6 (7.1)	0	10 (24.4)	0	0
Dysphonia	68 (35.1)	0	0	2 (2.1)	0	0	32 (38.1)	0	0	0	0	0
AST increased	39 (20.1)	0	0	8 (8.3)	0	0	25 (29.8)	1 (1.2)	0	6 (14.6)	1 (2.4)	0
TSH increased	51 (26.3)	0	0	1 (1.0)	0	0	18 (21.4)	0	0	2 (4.9)	0	0
Blood bilirubin increased	45 (23.2)	3 (1.5)	0	7 (7.3)	2 (2.1)	0	11 (13.1)	1 (1.2)	0	3 (7.3)	0	0
ALT increased	27 (13.9)	1 (0.5)	0	8 (8.3)	0	0	23 (27.4)	1 (1.2)	0	4 (9.8)	2 (4.9)	0
Diarrhea	31 (16.0)	4 (2.1)	0	3 (3.1)	0	0	25 (29.8)	4 (4.8)	0	0	0	0

Abbreviations: AST=aspartate aminotransferase, ALT=alanine aminotransferase; BSC=best supportive care; N=number of planned patients; n=number of patients; TSH=thyroid-stimulating hormone; VEGF=vascular endothelial growth factor; TEAE=treatment-emergent adverse event

CONCLUSIONS

- This subgroup analysis result is consistent with previously reported FRESCO intent-to-treat population results
- Fruquintinib showed clinically meaningful benefits in third-line mCRC patients regardless of prior target therapy without observed accumulative toxicity

Sponsor Information:

- This analysis was conducted by Eli Lilly Shanghai
- The FRESCO trial was sponsored by Hutchison MediPharma and co-funded by Eli Lilly company

References:

1. Liu S et al. *Chin J Cancer Res* 2015; 27(1):22-8.
2. Haggar FA et al. *Clin Colon Rectal Surg* 2009; 22(4):191-7.
3. Ferlay J et al. *Int J Cancer* 2015; 136(5):E359-86.
4. Chen W et al. *CA Cancer J Clin* 2016; 66(2):115-32.
5. National Comprehensive Cancer Network. NCCN Guidelines: *Colon cancer* v2. 2016.
6. Van Cutsem E et al. *Ann Oncol* 2010; 21 suppl 5:v93-7.
7. Sun Q et al. *Cancer Biol Ther* 2014; 15(12):1635-45.
8. Li J et al. *J Clin Oncol* 2017; 35(15 suppl):3508.