In-depth Analysis of the FRESCO Study: a Randomized, Double-blind, Phase III Trial Evaluating the Efficacy and Safety of Fruquintinib in Patients with 3+ Line Advanced Colorectal Cancer

Shukui QIN*, Jin LI*, Yuxian BAI, Yanhong DENG, Lei YANG, Zhen-Dong CHEN, Haijun ZHONG, Rui-Hua XU, Hongmin PAN, Weijian GUO, Yongqian SHU, Ying YUAN, Jianfeng ZHOU, Nong XU, Tianshu LIU, Dong MA, Changping WU, Ying CHENG, Jian-Ming XU, Donghui CHEN, Wei LI, Sanyuan SUN, Zhuang YU, Peiguo CAO, Lin SHEN, Haihui CHEN, Jiejun WANG, Shubin WANG, Hongbing WANG, Songhua Fan, Ye Hua, Weiguo Su

On behalf of all FRESCO Investigators

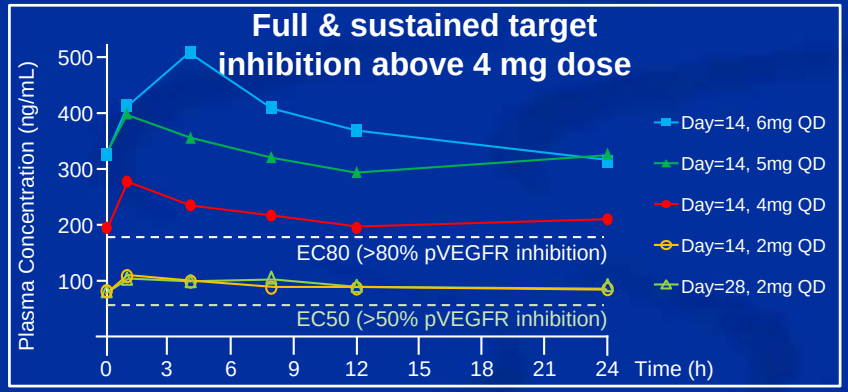
Fruquintinib:
a highly selective, potent inhibitor of VEGFR

VEGFR kinase activity[1]

Kinase assay	IC_{50} (nmol/L)
BIOCHEMICAL ACTIVITY	
VEGFR2 (KDR)	35 (25)
VEGFR3 (Flt4)	0.5
VEGFR1 (Flt1)	33
Ret	128
FGFR1	181
c-kit	458
Flt3	>10,000
PDGFRβ	>10,000
EGFR	>30,000
Tie2	>10,000
c-MET	>10,000
EphB4	>3,000
Akt	>3,000
CHK1	>10,000
CDK1	>10,000
CDK2	>10,000
CDK5	>10,000

Kinase assay	IC_{50} (nmol/L) or Inhibition rate (%)
CELL-BASED ACTIVITY	
bFGF stimulated p-FGFR1 in HUVEC	>1,000
VEGF-A stimulated p-VEGFR2 in HEK293	0.6 ± 0.2, n = 3
VEGF-C stimulated p-VEGFR3 in HLEC	1.5
VEGF-A dependent HUVEC proliferation	1.7
VEGF-C dependent HLEC proliferation	4.2
HUVEC tube formation	94% at 300 nmol/L
ANTI-ANGIOGENESIS ACTIVITY	
Chorioallantoic Membrane (CAM)	strong inhibition at 0.1 & 1 nmol/egg

- Highly selective and strong inhibition of VEGFR-1, 2, 3
- High drug exposure and full target inhibition at recommended dose[2]



[1] *Cancer Biol & Therapy, 15:12, 1635-1645 (2014)*

[2] *Cancer Chemother Pharmacol 2016; 78: 259-269*

Unmet clinical need of advanced CRC is urgent

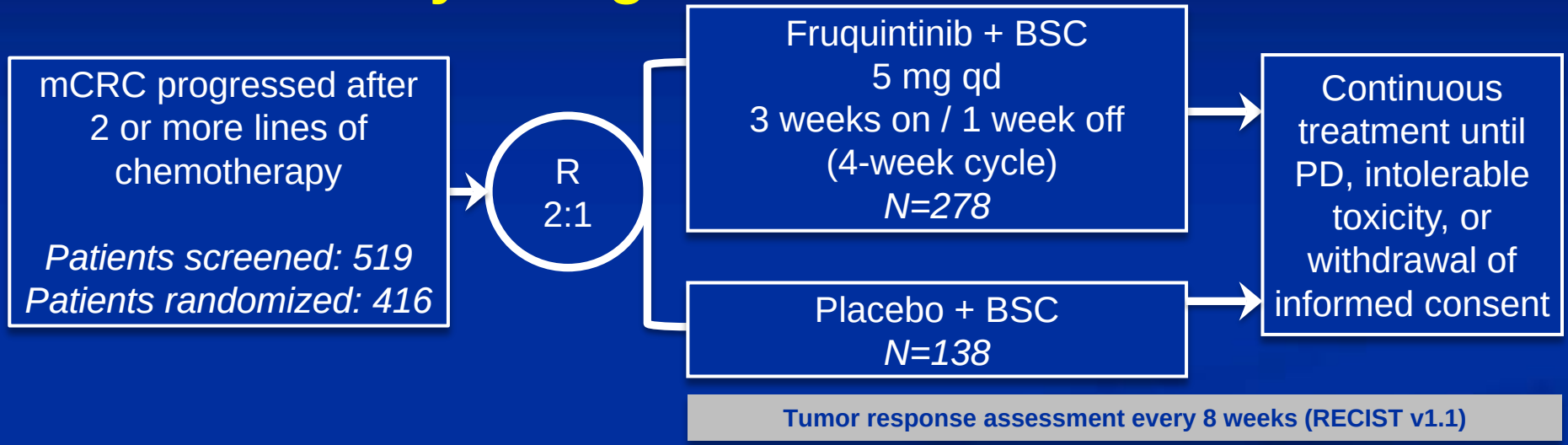
- **CRC is a highly prevalent malignant tumor**
  - Globally, 1.36 million new CRC cases and 694,000 deaths each year[3]
  - In China, 376,000 new CRC cases/year and the number is growing[4]
  - ~50% of the cases will develop into metastatic or advanced CRC[5,6]

- **Chemotherapies remain the cornerstone of systemic therapies for advanced CRC[3]**
  - Doublet chemotherapy regimens based on 5-Fu, OXA and CPT-11 are the 1st line and 2nd line standard chemotherapies for mCRC
  - Although recommended by NCCN, bevacizumab and cetuximab are used by only 10%~30% patients in China
  - Regorafenib was approved by FDA in 2014 and by CFDA in March 2017

- **Huge unmet clinical need**
  - Effective therapies after two lines of standard treatments for mCRC are quite limited[5]; most patients have a good constitution and a strong will to survive. The unmet clinical needs is huge

[3] *Int. J. Cancer, 136, E359-E386 (2015);* [4] *CA CANCER J CLIN 2016;66:115–132;* [5] *NCCN Guidelines. Colon cancer. v.2.2016;* [6] *Van Cutsem E et al. ESMO Guidelines 2010.*

FRESCO Study design



- Randomized, double-blind, placebo-controlled, multi-center phase III clinical study **(NCT02314819)**
  - Stratification factors: prior use of anti-VEGF therapies, K-Ras gene status
- Recruitment: Dec 2014 to May 2016
- Data cut-off: 17th Jan 2017

FRESCO study endpoints

- **Primary endpoint: overall survival (OS)**
  - 80% power to detect a hazard ratio (HR) of 0.7 (corresponding to a median OS improvement from 6.3 months to 9 months), 2-sided overall α=0.05
  - Planned sample size: 400

- **Key secondary endpoints:**
  - Progression-free survival (PFS)
  - Overall response rate (ORR)
  - Disease control rate (DCR)
  - Safety (NCI CTC 4.03)

Key inclusion criteria

- Aged 18-75 years
- Histologically and/or cytologically diagnosed with mCRC (Stage IV), excluding all other histological types
- Patients have failed at least 2 lines of standard chemotherapies, which must include 5-Fu, OXA and CPT-11
- Prior anti-VEGF or anti-EGFR targeted therapies are allowed, but patients with prior use of VEGFR inhibitors should be excluded
- ECOG PS 0-1, life expectancy ≥3 months
- Measurable lesion at baseline (RECIST v1.1)
- Adequate organ function (bone marrow, liver and renal function etc.)
- Patients have enough understanding of this study and with signed inform consent

Baseline characteristics

Baseline Characteristics		Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Age	<65 Years	228 (82.0)	110 (79.7)
	≥65 Years	50 (18.0)	28 (20.3)
Sex	Male	158 (56.8)	97 (70.3)
	Female	120 (43.2)	41 (29.7)
Ethnicity	Han	272 (97.8)	135 (97.8)
	Not Han	6 (2.2)	3 (2.2)
ECOG	0	77 (27.7)	37 (26.8)
	1	201 (72.3)	101 (73.2)

Baseline disease characteristics (1)

Disease Characteristics		Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Primary site of the disease	Colon	147 (52.9)	70 (50.7)
	Rectal	125 (45.0)	60 (43.5)
	Colon-Rectal	6 (2.1)	7 (5.1)
	Ileocecum	0	1 (0.7)
Primary location of tumor	Left	214 (77.0)	115 (83.3)
	Right	56 (20.1)	21 (15.2)
	Both or Unknown	8 (2.9)	2 (1.5)
K-RAS gene status	Wild type	157 (56.5)	74 (53.6)
	Mutant	121 (43.5)	64 (46.4)
Metastasis tumor site	Single	13 (4.7)	4 (2.9)
	Multiple	265 (95.3)	134 (97.1)
Liver Metastasis	Yes	185 (66.5)	102 (73.9)
	No	93 (33.5)	36 (26.1)

Baseline disease characteristics (2)

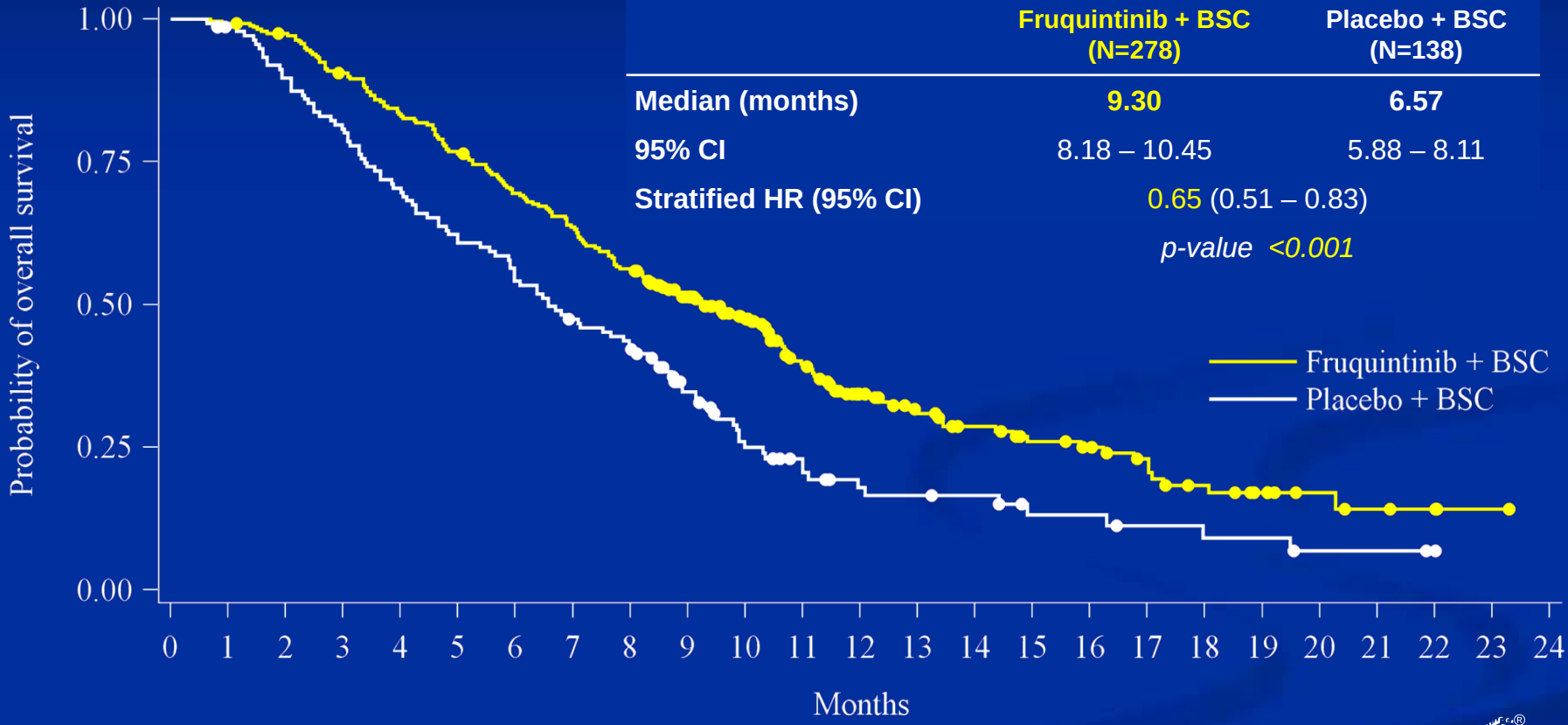
Disease Characteristics		Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Prior use of VEGFR inhibitor	Yes	84 (30.2)	41 (29.7)
	No	194 (69.8)	97 (70.3)
Prior use of EGFR inhibitor	Yes	40 (14.4)	19 (13.8)
	No	238 (85.6)	119 (86.2)
Prior targeted therapy (excluding VEGFR)	No anti-VEGF or anti-EGFR	167 (60.1)	83 (60.1)
	Anti-VEGF or anti-EGFR	111 (39.9)	55 (39.9)
Prior chemotherapies (number of treatment lines)	2-3	190 (68.3)	8 (71.0)
	>3	88 (31.7)	40 (29.0)

Overall Efficacy Analysis

Overall Survival (OS):

FRESCO successfully reached the pre-specified primary endpoint

	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*	



OS sensitivity analysis

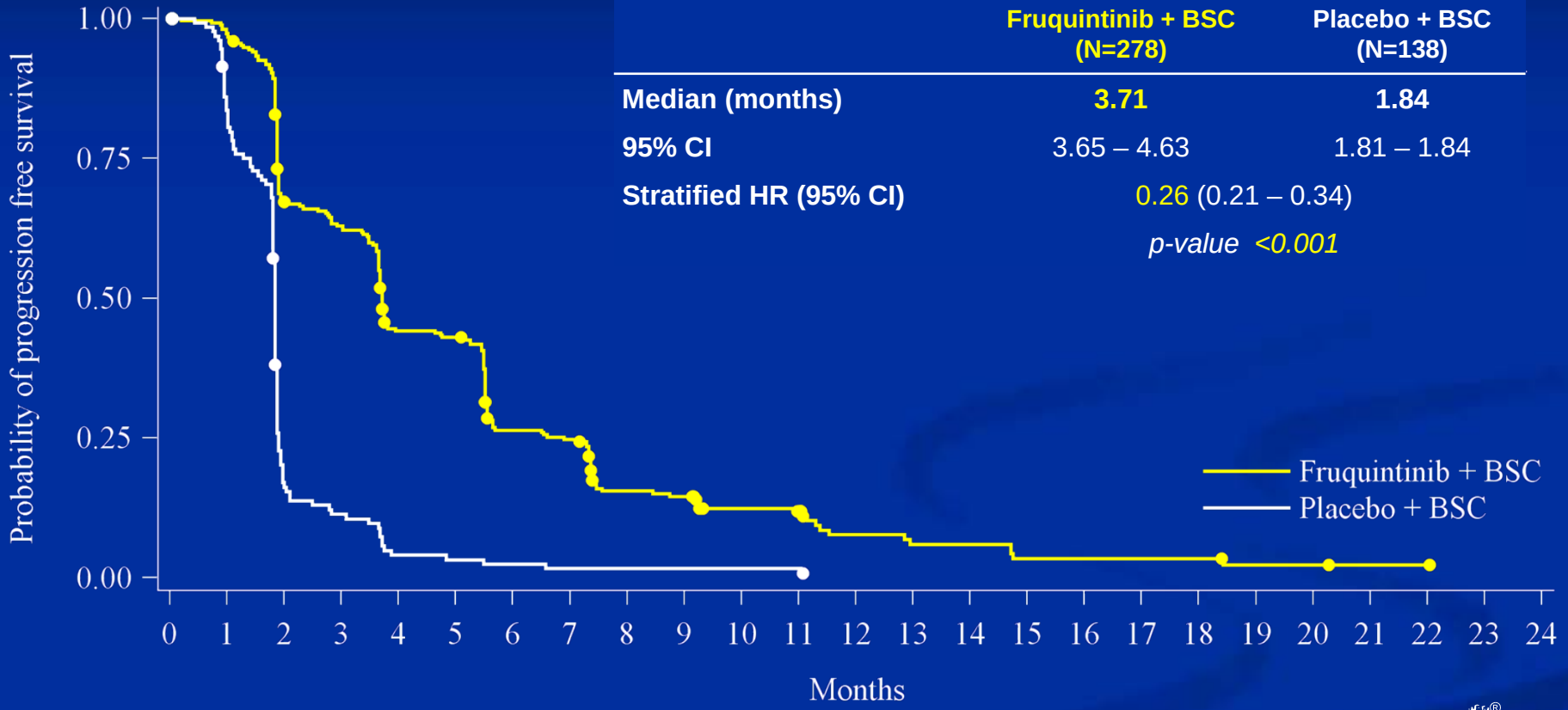
	Fruquintinib	Placebo
Per-protocol set (275:130)	9.3 months (95% CI: 8.2, 10.5)	6.8 months (95% CI: 5.9, 8.4)
	Stratified log-rank test ***P = 0.001***; stratified HR=0.66 (95% CI: 0.52, 0.85)	
Non-stratified analysis (278:138)	9.3 months (95% CI: 8.2, 10.5)	6.6 months (95% CI: 5.9, 8.1)
	Non-stratified log-rank test ***P < 0.001***; Non-stratified HR=0.62 (95% CI: 0.49, 0.79)	
Analysis adjusted for covariates*	HR=0.62 (95% CI: 0.49, 0.79), ***P < 0.001***	

* Stratification (stratification factors: prior use of anti-VEGF therapies, K-Ras gene status) Cox proportional hazards regression model, stepwise selection of variables that could affect the efficacy was conducted at a significance level of 0.1 and the effect of other baseline demographic characteristics and disease characteristics on OS was taken into consideration. Covariates that were included into the model were：liver metastasis (Yes vs No), time from 1st metastatic diagnosis to randomization, primary tumor site at the time of diagnosis, metastasis tumor site (multiple vs. single) and prior targeted therapy.

Progression-free Survival (PFS):

Fruquintinib significantly improved PFS compared with placebo

	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*	



Tumor Response

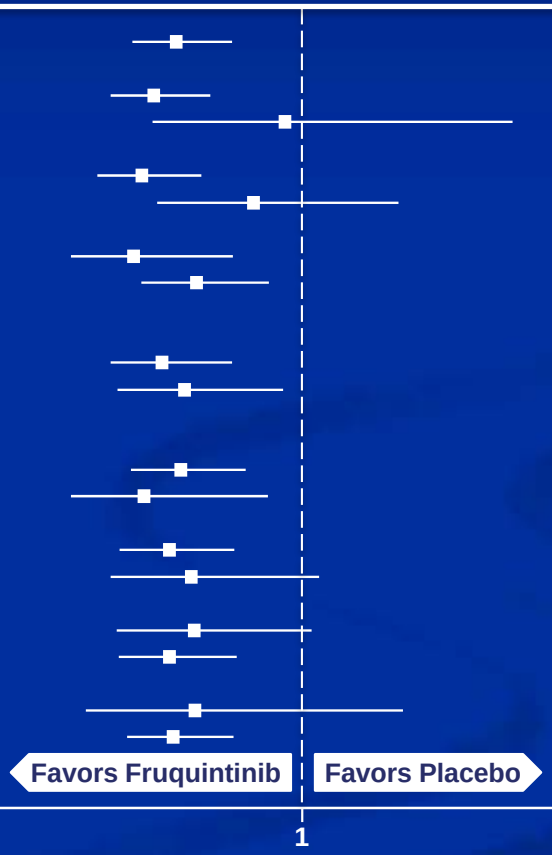
Best response	Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Complete Response (CR)	1 (0.4)	0
Partial Response (PR)	12 (4.3)	0
Stable Disease (SD)	160 (57.6)	17 (12.3)
Progressive Disease (PD)	87 (31.3)	98 (71.0)
Not done / not evaluated	18 (6.4)	23 (16.7)
Objective Response Rate (ORR)	13 (4.7)	0
Duration of Response (DoR, month)	>5.6 (5.6, -)	--
Disease Control Rate (DCR)	173 (62.2)	17 (12.3)
Duration of Disease Control [median, (95%CI, month)	5.6 (5.6, 5.7)	3.7 (3.7, 4.8)

*ORR = CR + PR (≥8 weeks confirmed), *P*=0.012；DCR = CR + PR + SD (≥8 weeks after randomization), *P*<0.001

Subgroup Analysis

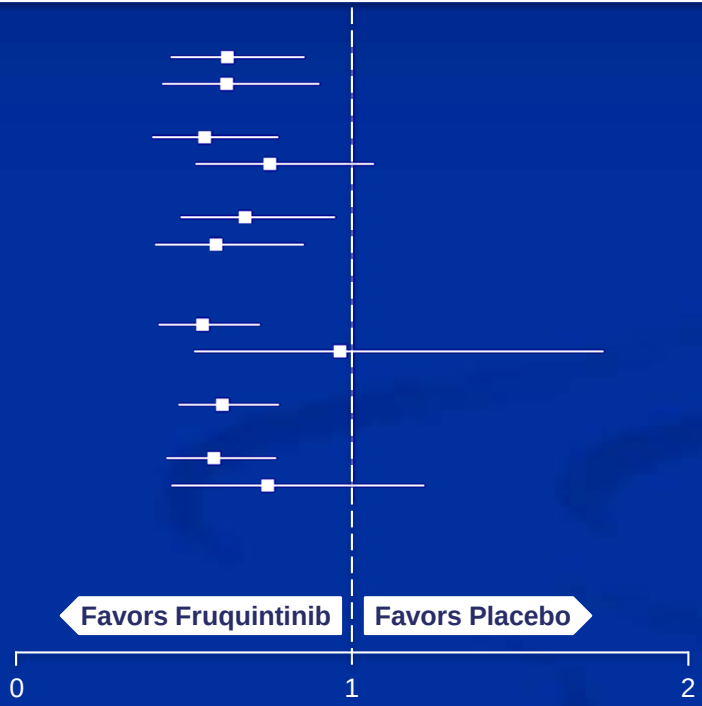
OS subgroup analysis-1

Subgroup	Fruquintinib	Placebo	HR (95% CI)
Overall	188/278	109/138	0.62 (0.49 – 0.79)
Age			
< 65	151/228	88/110	0.56 (0.43 – 0.73)
≥ 65	37/50	21/28	0.95 (0.55 – 1.63)
Gender			
Male	108/158	77/97	0.52 (0.39 – 0.70)
Female	80/120	32/41	0.85 (0.57 – 1.29)
Baseline ECOG Performance Status			
0	50/77	28/37	0.50 (0.31 – 0.79)
1	138/201	81/101	0.68 (0.52 – 0.90)
Time From 1st Metastatic Diagnosis to Randomization			
≤ 18 Months	115/163	64/75	0.58 (0.43 – 0.79)
> 18 Months	73/115	45/63	0.65 (0.45 – 0.94)
Number of Prior Treatment Line on or Above Metastatic Disease			
≤ 3	146/221	86/107	0.64 (0.49 – 0.83)
> 3	42/57	23/31	0.53 (0.31 – 0.90)
Previous Chemotherapy Lines			
2 or 3	126/190	80/98	0.60 (0.46 – 0.80)
> 3	62/88	29/40	0.67 (0.43 – 1.05)
Prior VEGF Inhibitors			
Yes	60/84	35/41	0.68 (0.45 – 1.03)
No	128/194	74/97	0.60 (0.45 – 0.80)
Prior Use Of EGFR Inhibitors			
Yes	31/40	14/19	0.68 (0.35 – 1.30)
No	157/238	95/119	0.62 (0.48 – 0.80)



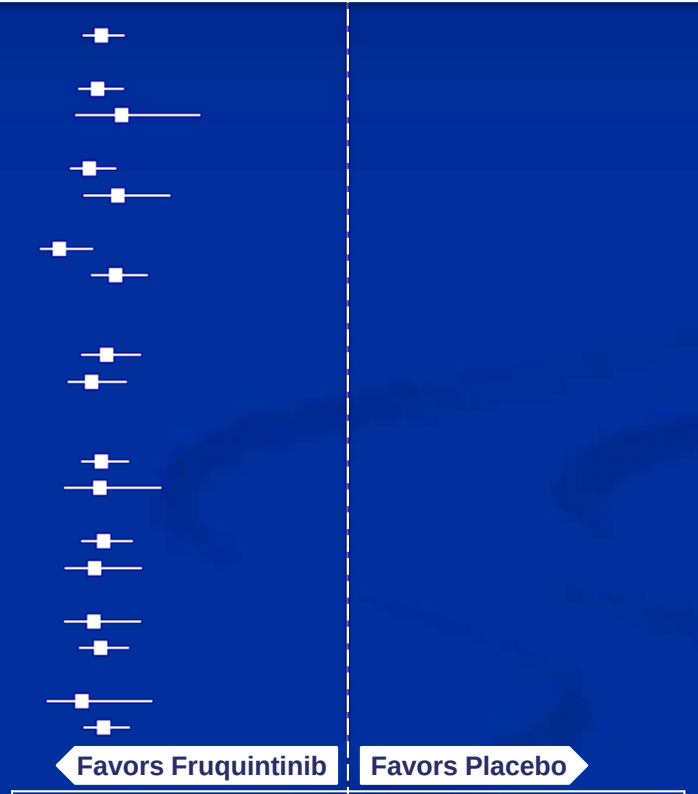
OS subgroup analysis-2

Subgroup	Fruquintinib	Placebo	HR (95% CI)
Prior Targeted Therapy			
No Anti-VEGF and No Anti-EGFR	109/167	63/83	0.63 (0.46 – 0.86)
Anti-VEGF or Anti-EGFR	79/111	46/55	0.63 (0.43 – 0.90)
K-Ras Gene Status			
Wild Type	103/157	56/74	0.56 (0.40 – 0.78)
Mutant Type	85/121	53/64	0.75 (0.53 – 1.07)
Primary Tumor Site			
Colon	98/147	55/70	0.68 (0.49 – 0.95)
Rectal	84/125	46/60	0.60 (0.41 – 0.86)
Primary Site at the Time of Diagnosis			
Left	141/214	91/115	0.56 (0.43 – 0.73)
Right	41/56	16/21	0.96 (0.53 – 1.75)
Metastasis Tumor Site			
Multiple	183/265	107/134	0.61 (0.48 – 0.78)
Liver Metastasis			
Yes	134/185	85/102	0.59 (0.45 – 0.77)
No	54/93	24/36	0.75 (0.46 – 1.21)



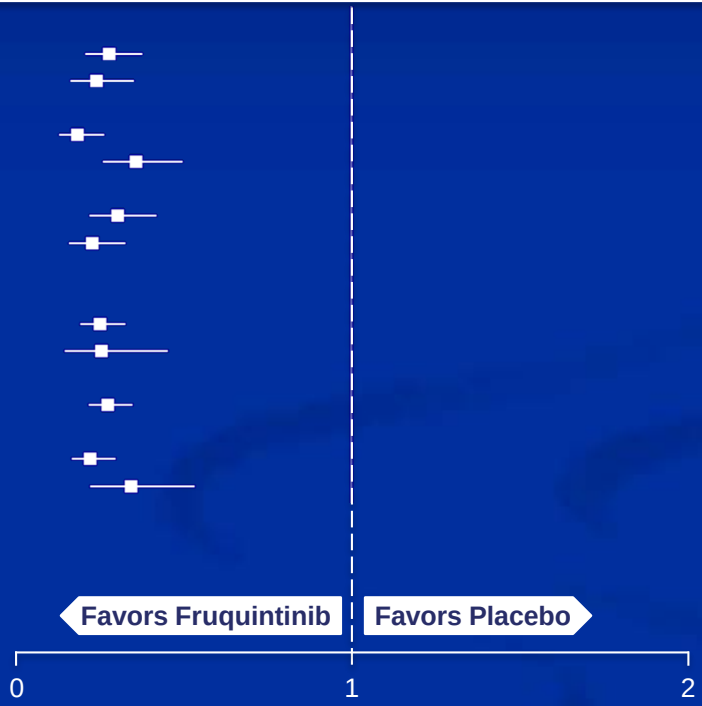
PFS subgroup analysis-1

Subgroup	Fruquintinib	Placebo	HR (95% CI)
Overall	235/278	125/138	0.27 (0.21 – 0.34)
Age			
< 65	189/228	101/110	0.26 (0.20 – 0.33)
≥ 65	46/50	24/28	0.33 (0.19 – 0.56)
Gender			
Male	137/158	88/ 97	0.23 (0.17 – 0.31)
Female	98/120	37/ 41	0.32 (0.21 – 0.47)
Baseline ECOG Performance Status			
0	63/77	32/37	0.14 (0.08 – 0.24)
1	172/201	93/101	0.31 (0.24 – 0.40)
Time From 1st Metastatic Diagnosis to Randomization			
≤ 18 Months	140/163	68/75	0.28 (0.21 – 0.38)
> 18 Months	95/115	57/63	0.24 (0.17 – 0.34)
Number of Prior Treatment Line on or Above Metastatic Disease			
≤ 3	185/221	99/107	0.27 (0.21 – 0.35)
> 3	50/57	26/31	0.26 (0.15 – 0.45)
Previous Chemotherapy Lines			
2 or 3	160/190	91/ 98	0.27 (0.21 – 0.36)
> 3	75/ 88	34/ 40	0.25 (0.16 – 0.39)
Prior VEGF Inhibitors			
Yes	70/84	36/41	0.24 (0.15 – 0.38)
No	165/194	89/97	0.26 (0.20 – 0.35)
Prior Use Of EGFR Inhibitors			
Yes	36/40	16/19	0.21 (0.10 – 0.42)
No	199/238	109/119	0.27 (0.21 – 0.35)



PFS subgroup analysis-2

Subgroup	Fruquintinib	Placebo	HR (95% CI)
Prior Targeted Therapy			
No Anti-VEGF and No Anti-EGFR	140/167	75/83	0.28 (0.21 – 0.37)
Anti-VEGF or Anti-EGFR	95/111	50/55	0.24 (0.16 – 0.35)
K-Ras Gene Status			
Wild Type	133/157	65/74	0.18 (0.13 – 0.26)
Mutant Type	102/121	60/64	0.36 (0.26 – 0.50)
Primary Tumor Site			
Colon	125/147	64/70	0.30 (0.22 – 0.42)
Rectal	105/125	53/60	0.23 (0.16 – 0.33)
Primary Site at the Time of Diagnosis			
Left	182/214	102/115	0.25 (0.19 – 0.33)
Right	45/56	21/21	0.25 (0.14 – 0.45)
Metastasis Tumor Site			
Multiple	225/265	122/134	0.27 (0.22 – 0.35)
Liver Metastasis			
Yes	160/185	95/102	0.22 (0.17 – 0.30)
No	75/93	30/36	0.34 (0.22 – 0.53)



Subgroup Analysis of Prior Use of Anti-VEGF or Anti-EGFR Therapies on Efficacy

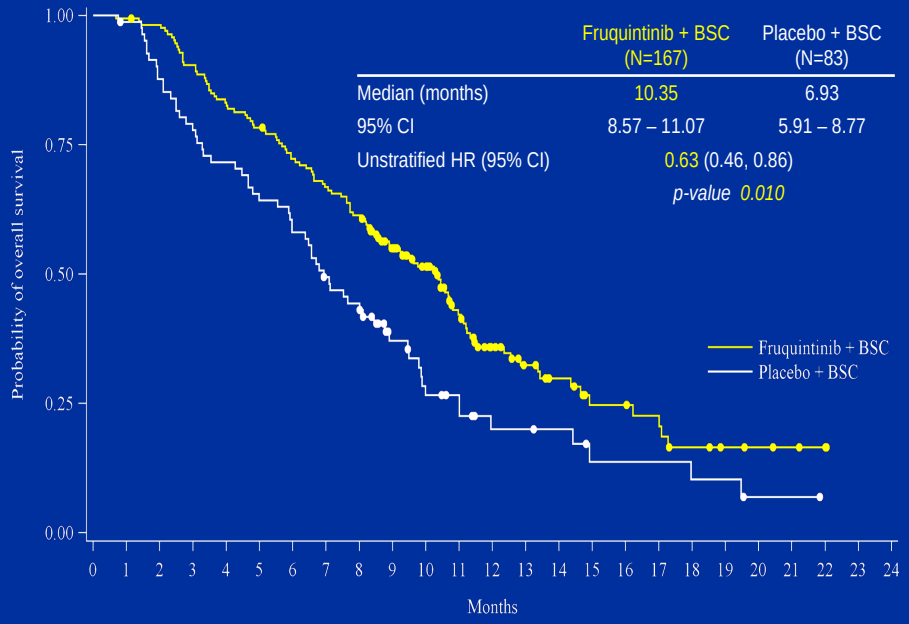
Effect of prior targeted therapy on efficacy

		Fruquintinib (n=278)	Placebo (n=138)	HR (95%CI)
Prior targeted therapy, %	No anti-VEGF or anti-EGFR	60	60	NA
	Prior use of anti-VEGF or anti-EGFR	40	40	NA
mOS, month	No anti-VEGF or anti-EGFR	10.4	6.9	0.63 (0.46, 0.86)
	Prior use of anti-VEGF or anti-EGFR	7.7	6.0	0.63 (0.43, 0.90)
mPFS, month	No anti-VEGF or anti-EGFR	3.8	1.8	0.28 (0.21, 0.37)
	Prior use of anti-VEGF or anti-EGFR	3.7	1.8	0.24 (0.16, 0.37)

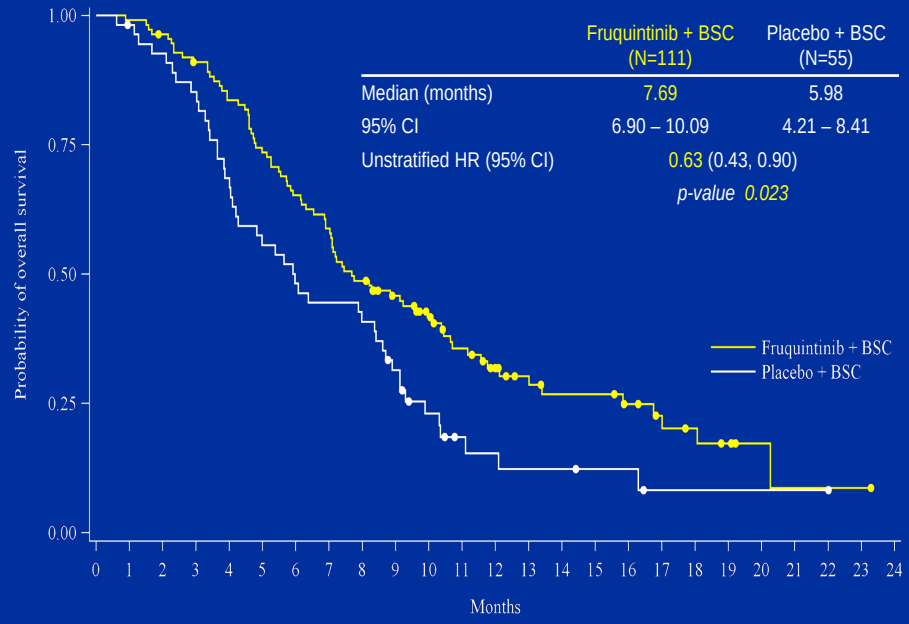
- In the subgroup analysis of patients with or without prior targeted therapy, OS and PFS were significantly improved by Fruquintinib, regardless of whether or not anti-VEGF or anti-EGFR had been used

Effect of prior targeted therapy on OS

Patients who never received targeted therapy (167:83): mOS of the Fruquintinib group was significantly improved (10.4m *vs* 6.9m; HR = 0.63)

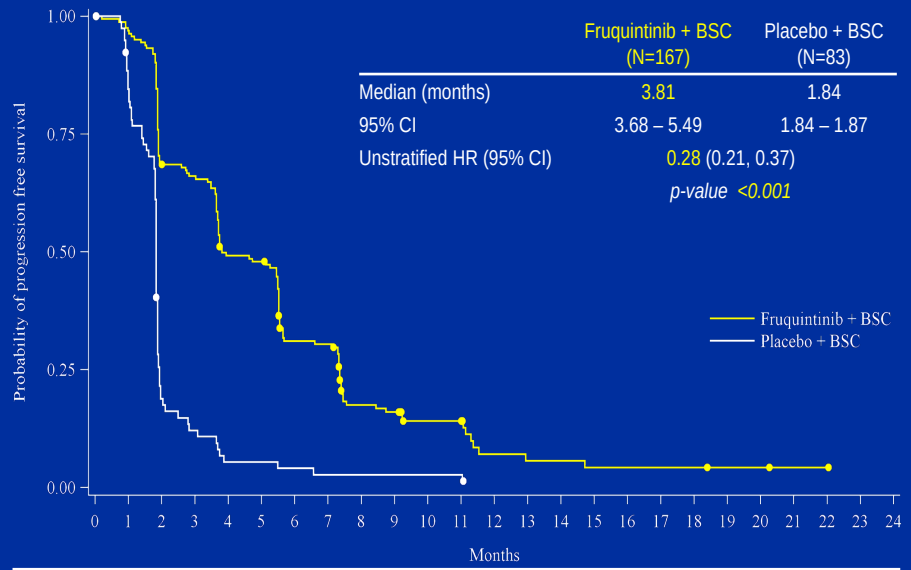


Patients who had received prior targeted therapy (111:55): mOS of the Fruquintinib group was also significantly improved (7.7m *vs* 6.0m; HR=0.63)



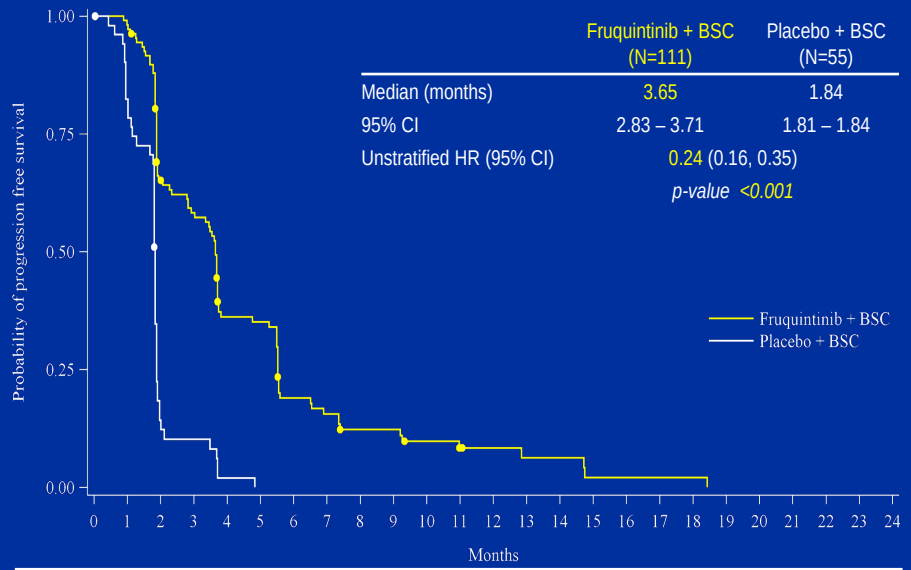
Effect of prior targeted therapy on PFS

For patients who never received targeted therapy (167:83), mPFS was significantly improved for the fruquintinib group (3.8m vs 1.8m, HR=0.28)



No prior use of targeted therapy	Fruquintinib N=167	Placebo N=83
ORR* n(%)	9 (5.4)	0
DoR	>5.5 (5.5-)	--
DCR, n(%)	108 (64.7)	11 (13.3)
Duration of disease control	5.6 (5.5-7.3)	3.8 (3.6-6.6)

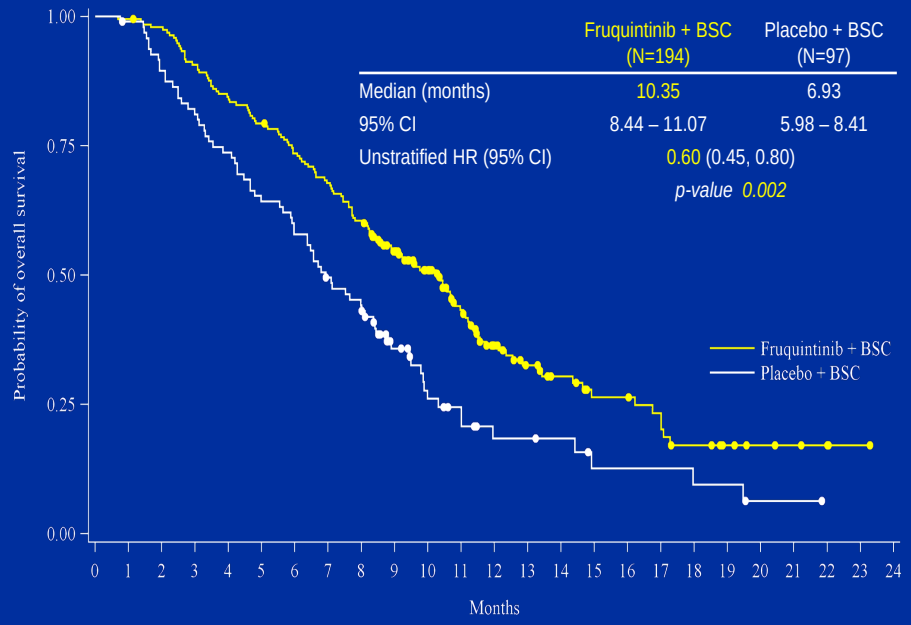
For patients who had received prior targeted therapy (111:55), mPFS was also significantly improved for the fruquintinib group (3.7m vs 1.8 m, HR=0.24)



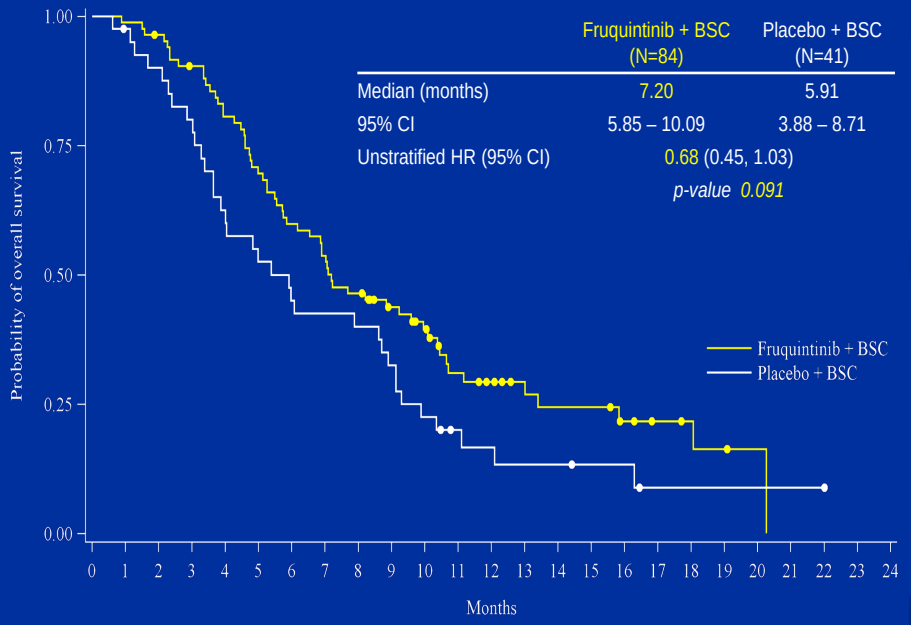
Prior use of targeted therapy	Fruquintinib N=111	Placebo N=55
ORR* n(%)	4 (3.6)	0
DoR	>7.5 (7.5-)	--
DCR, n(%)	65 (58.6)	6 (10.9)
Duration of disease control	5.5 (3.7,5.5)	3.7 (3.5,4.8)

Effect of prior use of anti-VEGF on OS

For patients who never received anti-VEGF (194:98), mOS of the fruquintinib group was significantly improved (10.4m vs 6.9m, HR=0.60)



For patients who had received prior anti-VEGF (84:40), mOS of the fruquintinib group was also significantly improved (7.2m vs 5.9m, HR=0.68)



Subgroup Analysis of K-RAS Gene Status on OS

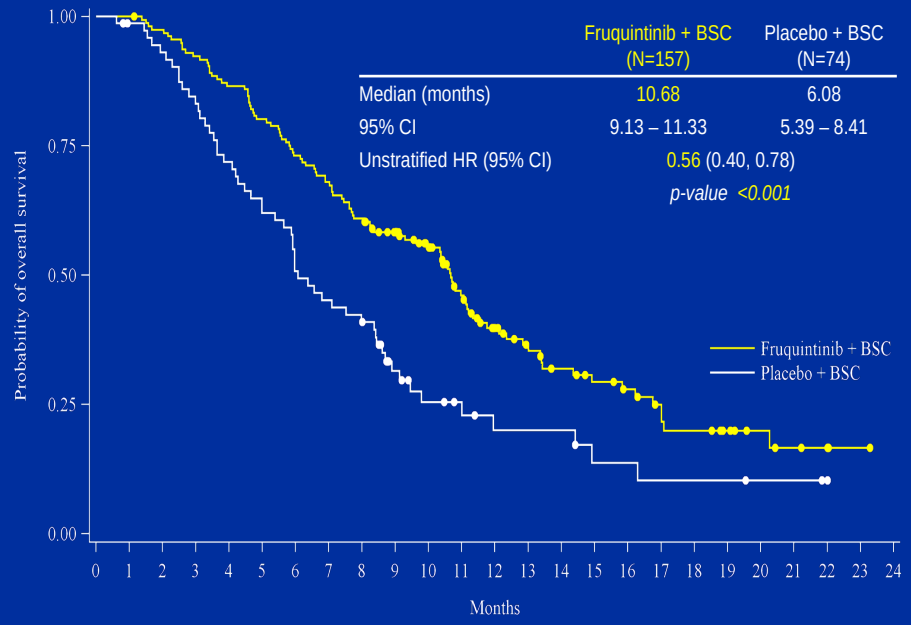
Subgroup analysis of K-RAS gene status on efficacy

		Fruquintinib (n=278)	Placebo (n=138)	HR(95%CI)
KRAS gene status,%	KRAS WT	56.5	53.6	NA
	KRAS m+	43.5	46.4	NA
mOS, month	KRAS WT	10.7	6.1	0.56 (0.40, 0.78)
	KRAS m+	8.2	7.0	0.75 (0.53, 1.07)
mPFS, month	KRAS WT	3.8	1.8	0.18 (0.13, 0.26)
	KRAS m+	3.8	1.8	0.36 (0.26, 0.50)

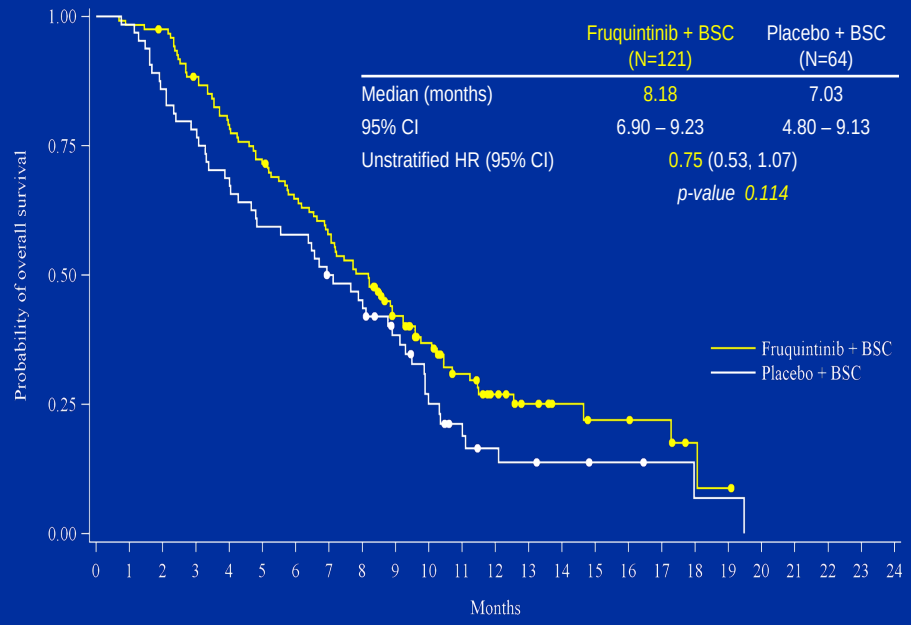
Fruquintinib group: In the subgroup analysis of K-RAS gene status, OS and PFS were both improved. In this study, KRAS gene status was not a prognostic factor for fruquintinib treatment

Subgroup analysis of K-RAS gene status on OS

For patients who were K-RAS WT (157:74), fruquintinib significantly improved mOS (10.7m vs 6.1m, HR=0.56)



For patients who were K-RAS m+ (121:64), fruquintinib also improved mOS (8.2m vs 7.0m, HR=0.75)



Following anti-tumor treatment of the two groups

	Fruquintinib (N=278) n(%)	Placebo (N=138) n(%)
Patients with following anti-tumor treatment, n (%)	118 (42.4)	70 (50.7)
Following anti-tumor treatment types		
chemotherapy	90 (32.4)	61 (44.2)
radiotherapy	19 (6.8)	6 (4.3)
surgery	13 (4.7)	6 (4.3)
others	44 (15.8)	23 (16.7)
Following targeted therapy		
only VEGF/VEGFR inhibitors	30 (10.8)	22 (15.9)
only EGFR inhibitors	8 (2.9)	6 (4.3)
Concurrent VEGF/VEGFR and EGFR inhibitors	4 (1.4)	0
Other study drugs	7 (2.5)	14 (10.1)

Drug exposure
(safety population)

	Fruquintinib (N=278)	Placebo (N=137)
Drug exposure (month)		
mean (SD)	4.9 (3.97)	1.9 (1.52)
median (min, max)	3.7 (0.1, 21.9)	1.8 (0.1, 11.1)
Treatment cycles		
mean (SD)	5.5 (4.28)	2.2 (1.61)
median (min, max)	4.0 (1, 24)	2.0 (1, 12)
Dose intensity (mg)		
mean (SD)	3.5 (0.55)	3.7 (0.49)
median (min, max)	3.70 (1.5, 5.0)	3.80 (1.5, 5.0)
Relative dose intensity		
mean (SD)	0.92 (0.14)	0.98 (0.13)
median (min, max)	1.0 (0.4, 1.3)	1.0 (0.4, 1.3)

Treatment-emergent AEs Overview
(safety population)

Adverse Events (NCI CTCAE 4.03)	Fruquintinib (N=278) n (%)	Placebo (N=137) n (%)
Any Grade	274 (98.6)	121 (88.3)
Grade 3	149 (53.6)	23 (16.8)
Grade 4	12 (4.3)	2 (1.5)
Grade 5	9 (3.2)	2 (1.5)
Grade ≥3	170 (61.1)	27 (19.7)
SAE	43 (15.5)	8 (5.8)
Leading to		
dose interruption	98 (35.3)	14 (10.2)
dose reduction	67 (24.1)	6 (4.4)
dose interruption or reduction	131 (47.1)	18 (13.1)
treatment discontinuation	42 (15.1)	8 (5.8)

Drug-related treatment-emergent AEs
(safety population; occurred in >15% patients)

Adverse Events	Fruquintinib (N=278) n (%)			Placebo (N=137) n (%)		
	All grades	Grade 3-4	Grade 5	All grades	Grade 3-4	Grade 5
Hypertension	154 (55.4)	59 (21.2)	0	21 (15.3)	3 (2.2)	0
PPE (or HFSR)	137 (49.3)	30 (10.8)	0	4 (2.9)	0	0
Proteinuria	117 (42.1)	9 (3.2)	0	34 (24.8)	0	0
Dysphonia	100 (36.0)	0	0	2 (1.5)	0	0
Weight decreased	59 (21.2)	4 (1.4)	0	12 (8.8)	0	0
Diarrhea	56 (20.1)	8 (2.9)	0	3 (2.2)	0	0
Stomatitis	47 (16.9)	1 (0.4)	0	0	0	0
Decreased appetite	45 (16.2)	3 (1.1)	0	11 (8.0)	0	0
Hypothyroidism	43 (15.5)	0	0	3 (2.2)	0	0
TSH increased	69 (24.8)	0	0	3 (2.2)	0	0
AST increased	64 (23.0)	1 (0.4)	0	14 (10.2)	1 (0.7)	0
Bilirubin increased	56 (20.1)	4 (1.4)	0	10 (7.3)	2 (1.5)	0
ALT increased	50 (18.0)	2 (0.7)	0	12 (8.8)	2 (1.5)	0

FRESCO Results

- The study met all pre-specified endpoints

  Fruquintinib vs. placebo:

  - **OS: 9.30 vs. 6.57 m (HR=0.65, P<0.001)**
  - **PFS: 3.71 vs. 1.84 m (HR=0.26, P<0.001)**
  - **ORR: 4.7% vs. 0 (P=0.012)**
  - **DCR: 62.2% vs. 12.3% (P<0.001)**

- All pre-specified subgroup analyses showed consistent tendency for improved OS and PFS with fruquintinib
  - **Significant survival benefit of fruquintinib demonstrated, regardless of whether patients received prior anti-VEGF / anti-EGFR treatment**
  - **For patients who had not received anti-VEGF treatment, fruquintinib improved the mOS to 10.4 months; for patients who had received prior anti-VEGF treatment, fruquintinib reduced the mortality risk by 32%**
  - **For patients who were K-RAS WT, fruquintinib improved the mOS to 10.7 months; for patients who were K-RAS m+, fruquintinib reduced the mortality risk by 25%**
- Relatively good safety profile
  - **Most frequent Grade 3 or above AEs were target-related, such as hypertension, PPE and proteinuria, and clinically manageable**
  - **Grade 3/4 hepatic toxicities were found similar to placebo**

Conclusions

- Fruquintinib significantly improved mOS for nearly three months and mPFS for nearly two months in patients with 3rd line advanced CRC; ORR and DCR were significantly improved as well
- Overall and subgroup analyses of OS and PFS demonstrated that the efficacy of fruquintinib in patients with 3rd line advanced CRC was stable and consistent
- Fruquintinib showed a good safety profile with manageable AEs and without unexpected serious safety flags
- Fruquintinib has the potential to become a standard treatment for 3rd line advanced CRC

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*Contributed equally to this work

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