FRESCO: A Phase III trial evaluating Fruquintinib efficacy and safety in 3+ line colorectal cancer patients

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On behalf of the FRESCO Investigators

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Disclosure

For Presenter: no conflicts of interest

The burden of metastatic CRC

Large patient population

- Globally, 1.36 million new CRC cases and over 694,000 deaths each year[1]
- China, 376,000 new CRC patients/year and growing[2]

Chemotherapies remain main stream therapy in China[3]

- Chemotherapy (fluoropyrimidines, oxaliplatin, irinotecan)
- Monoclonal antibodies (bevacizumab, cetuximab or panitumumab)
- Regorafenib approved for 3rd line patients recently

Limited standard salvage therapy available in China after two lines of standard chemotherapies[3]

High unmet clinical need for treatment options for mCRC, especially in China

1. Int. J. Cancer, 136, E359-E386 (2015); 2. CA CANCER J CLIN 2016;66:115–132 3. NCCN Guidelines. Colon cancer. v.2.2016

Fruquintinib: an oral, potent and highly selective VEGFR inhibitor

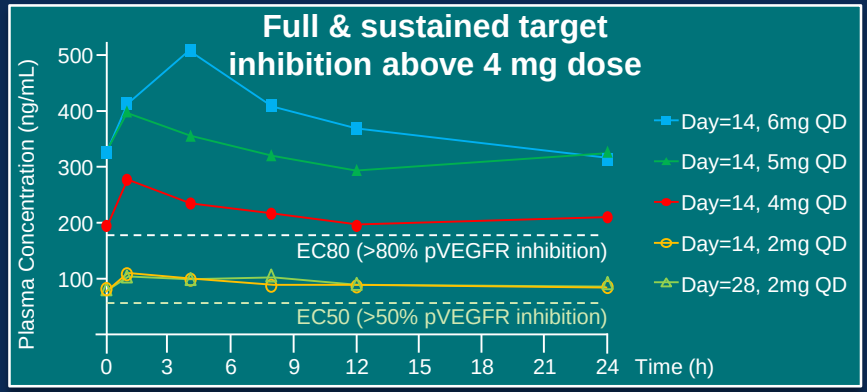
Fruquintinib kinase profile

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

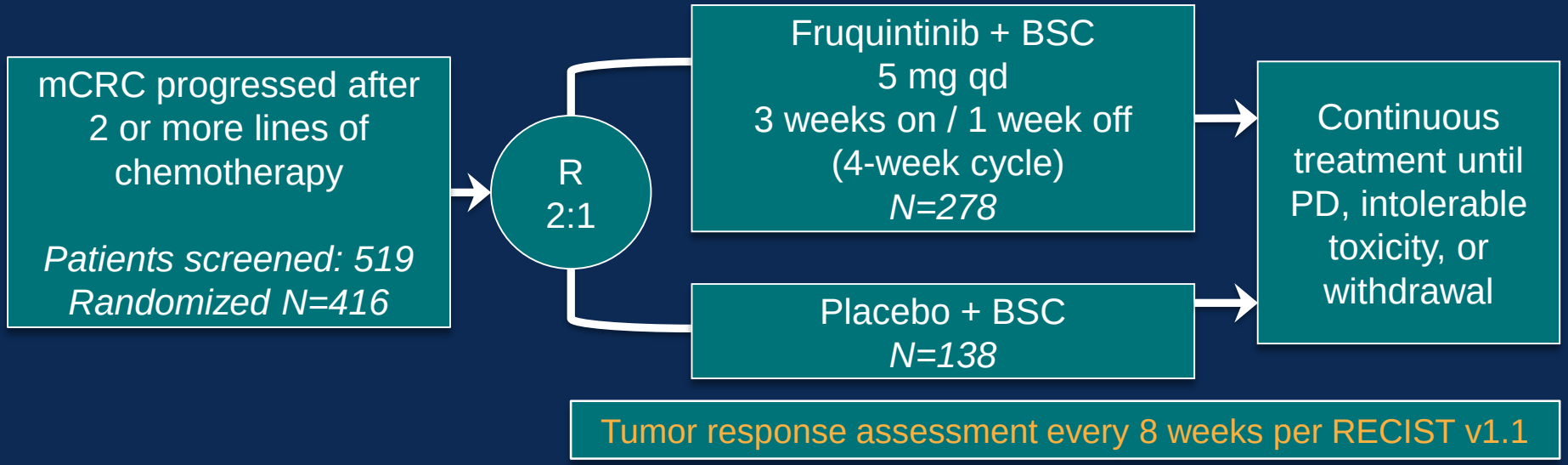
Kinase assay	IC_{50} (nmol/L) or Inhibition rate (%)
CELL-BASED ACTIVITY	
bFGF stimulated p-FGFR1 in HUVEC	>1,000
VEGF-A stimulated p-VEGFR2 in HEK293	0.6 ± 0.2, n = 3
VEGF-C stimulated p-VEGFR3 in HLEC	1.5
VEGF-A dependent HUVEC proliferation	1.7
VEGF-C dependent HLEC proliferation	4.2
HUVEC tube formation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

Cancer Biol & Therapy, 15:12, 1635-1645 (2014)

- Potent anti-VEGFR-1, 2 and 3
- Highly selective against other kinases
- High drug exposures at recommended clinical dose resulting in expected full and sustained target coverage
- Clean CYP profile suitable for combinations



FRESCO Study (NCT02314819)



- Multicenter, randomized, double-blind, placebo-controlled, phase III
  - Stratification factor: prior anti-VEGF therapy, K-Ras gene status
- Recruitment: Dec 2014 to May 2016
- Data cut-off: 17th Jan 2017

FRESCO Endpoints

- **Primary endpoint: overall survival (OS)**
  - 80% power to detect a hazard ratio 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)

Patient Eligibility: key inclusion criteria

- Histologically and/or cytologically diagnosed with metastatic CRC (Stage IV)
- Had failed 2 prior treatments with fluoropyrimidine, oxaliplatin, and irinotecan
- Prior anti-VEGF or anti-EGFR targeted therapy allowed, but not mandatory
- Age 18-75 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, life expectancy ≥3 months
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Adequate bone marrow, liver and renal function
- Signed inform consent

Demographic and Other Baseline Characteristics

Demographics		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)

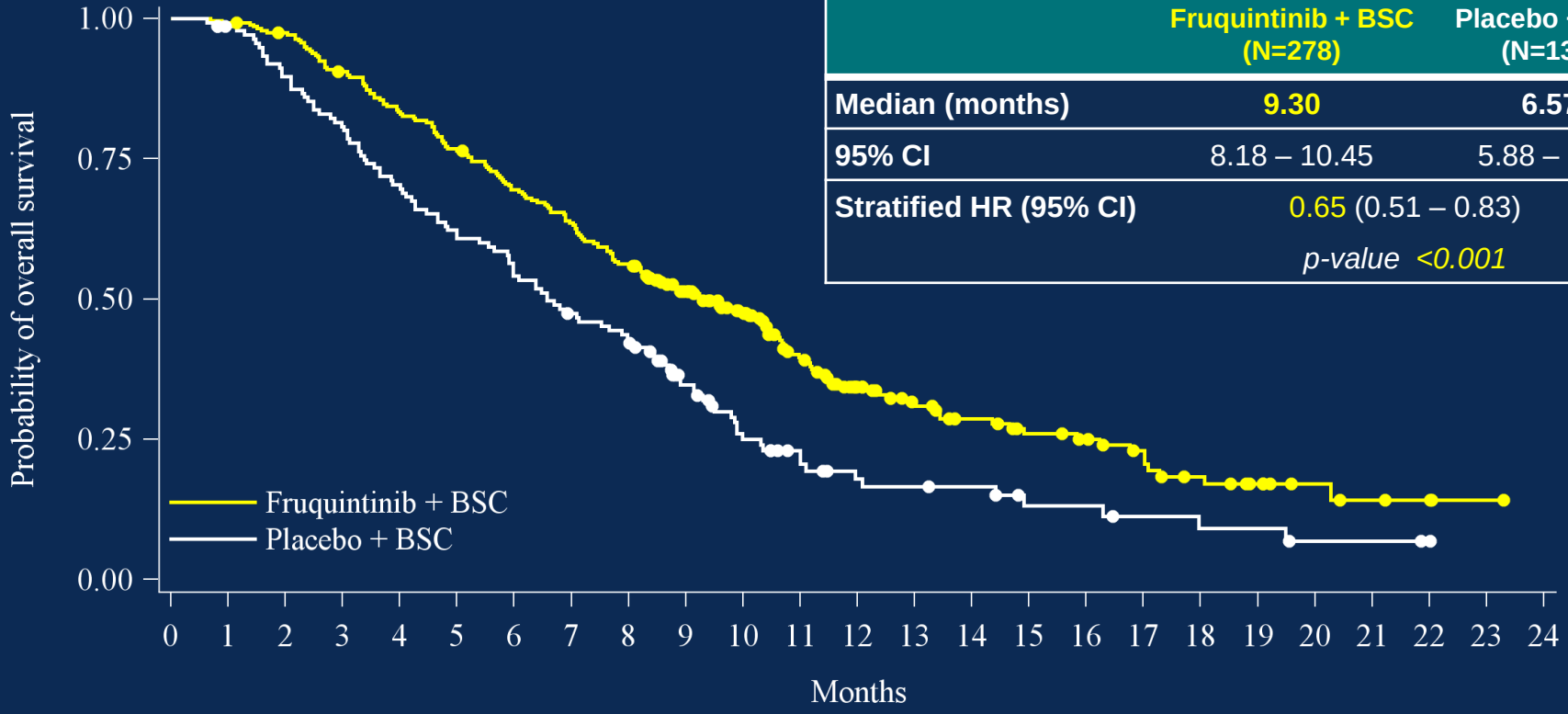
Baseline Disease Characteristics

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)
	Other #	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)
Prior use of VEGF 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)
Liver Metastasis	Yes	185 (66.5)	102 (73.9)
	No	93 (33.5)	36 (26.1)

ileocecal junction

Overall Survival (Primary Endpoint)

FRESCO clearly succeeded in meeting the primary efficacy endpoint of OS

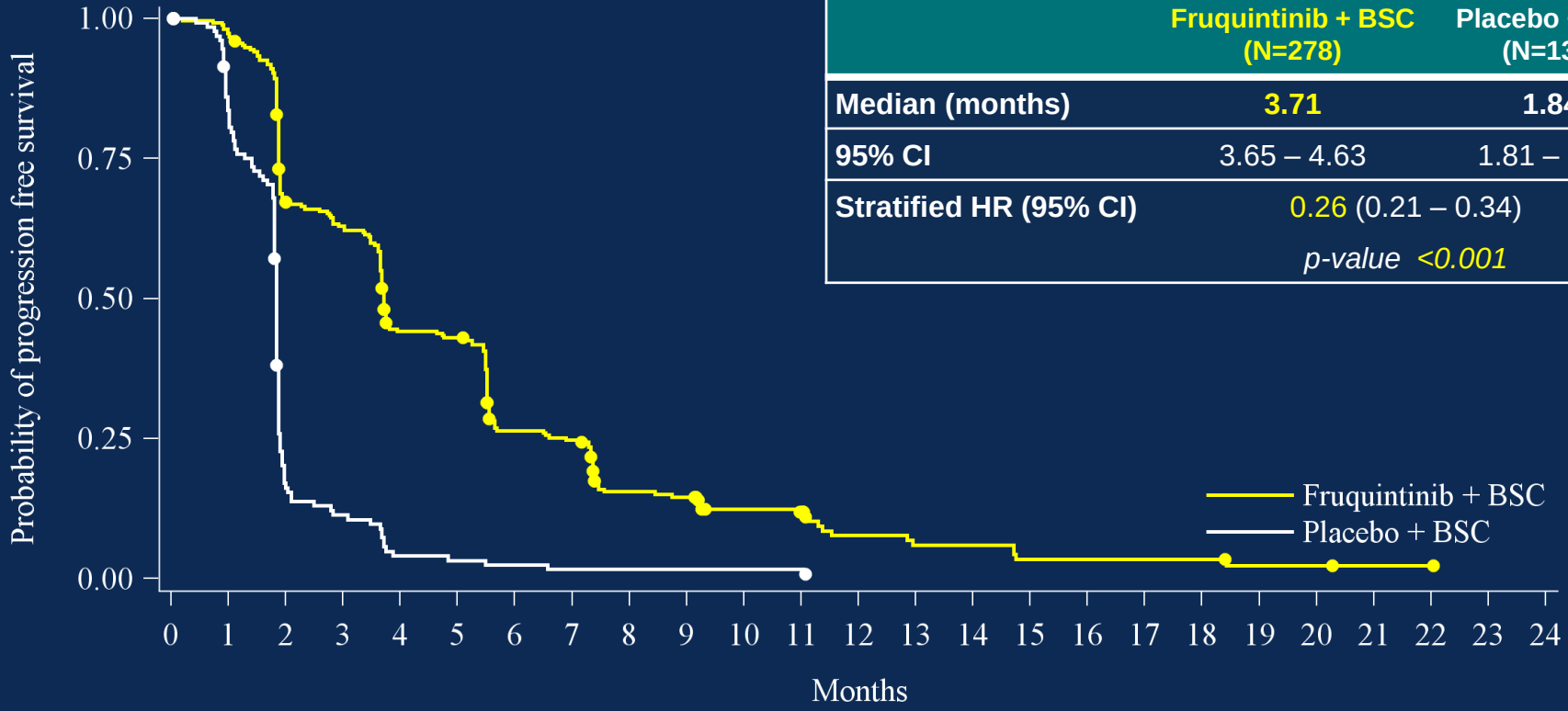


	Fruquintinib + BSC (N=278)	Placebo + BSC (N=138)
Median (months)	**9.30**	**6.57**
95% CI	8.18 – 10.45	5.88 – 8.11
Stratified HR (95% CI)	0.65 (0.51 – 0.83)	
	p-value *<0.001*	

Progression-free Survival

Fruquintinib significantly improves PFS compared to 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)
ORR	13 (4.7)	0
DCR	173 (62.2)	17 (12.3)

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

Drug Exposure (safety population)

	Fruquintinib (N=278)	Placebo (N=137)
Drug exposure (months)		
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 Adverse Events Overview
(safety population)

Adverse Events	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 Adverse Events
(safety population; occurring in >15% patients)

Preferred Term	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
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
Weight decreased	59 (21.2)	4 (1.4)	0	12 (8.8)	0	0
Bilirubin increased	56 (20.1)	4 (1.4)	0	10 (7.3)	2 (1.5)	0
Diarrhea	56 (20.1)	8 (2.9)	0	3 (2.2)	0	0
ALT increased	50 (18.0)	2 (0.7)	0	12 (8.8)	2 (1.5)	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

Summary of FRESCO Results

The study met all primary and secondary endpoints at the pre-planned analyses

Fruquintinib vs. placebo:

- **OS: 9.30 vs. 6.57 months, HR=0.65, $p<0.001$**
- **PFS: 3.71 vs. 1.84 months, HR=0.26, $p<0.001$**
- **ORR: 4.7% vs. 0, $p=0.012$**
- **DCR: 62.2% vs. 12.3%, $p<0.001$**

Acceptable safety profile

- **Most frequent Grade 3 AEs were target-related AEs, such as hypertension, PPE and proteinuria, and manageable**
- **Grade 3 hepatic toxicities were found similar to placebo**

Well tolerated with moderate rate of dose interruptions or reductions

Conclusions

- Fruquintinib significantly extended survival time in mCRC patients who have had failed at least 2 lines of systemic therapy
- Clinically meaningful and statistically significant benefits are also shown in PFS, ORR, DCR
- Fruquintinib is well tolerated in mCRC patients with a good safety profile that is consistent to other fruquintinib trials
- Fruquintinib demonstrated favorable risk-to-benefit balance in patients with mCRC

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