Adverse Events of Special Interest Profiles and Time Courses of Fruquintinib in the FRESCO Trial

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Disclosure

- For presenter: No conflict of interest
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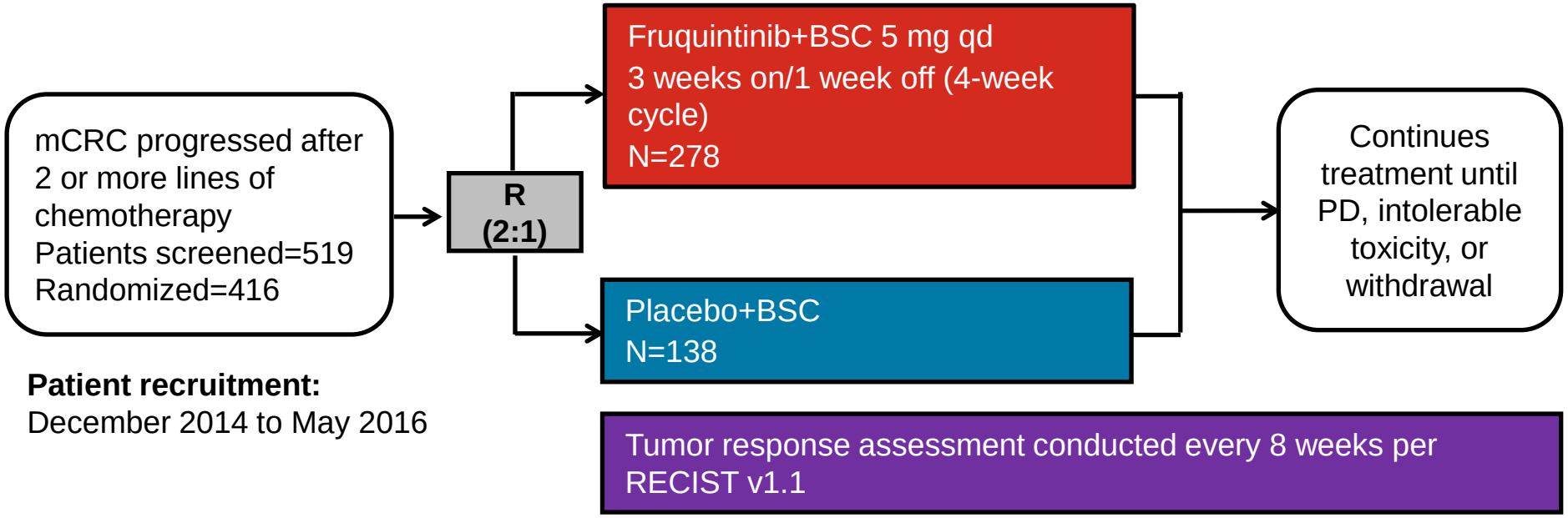
Background and Objective

- Treatment options for third-line metastatic colorectal cancer (mCRC) patients remain limited in China[1]
- Fruquintinib is a highly selective and potent oral inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2, and 3[2]; in the Phase III FRESCO trial, fruquintinib demonstrated a statistically significant and clinically meaningful overall survival benefit in Chinese patients with mCRC; fruquintinib was well tolerated, and the safety profile was consistent with that of its class[1]
- The objective of the present study was to elucidate in-depth fruquintinib predefined adverse events of special interest (AESI) in the FRESCO trial, including hypertension, dermatological toxicity, proteinuria, hemorrhage, thyroid dysfunction, cardiac ischemia and infarction, arterial/venous thromboembolic events, hepatotoxicity, and gastrointestinal perforation
- The drug-related AESI were summarized for each category; time-to-onset and frequency by treatment cycles on patients who had received at least 1 dose of study drug were analyzed

1. Li J et al. *J Clin Oncol* 2017;35(15_suppl):3508
2. Sun Q et al. *Cancer Biol Ther* 2014;15:1635-45

FRESCO Trial (NCT02314819)



Patient recruitment:
December 2014 to May 2016

Overall Survival

	Fruquintinib+BSC (N=278)	Placebo+BSC (N=138)
Median (months)	9.30	6.57
95% CI	8.08-10.45	5.65-8.11
Stratified HR (95% CI)	0.65 (0.51-0.83)	
p-value	<.001	

Progression-Free Survival

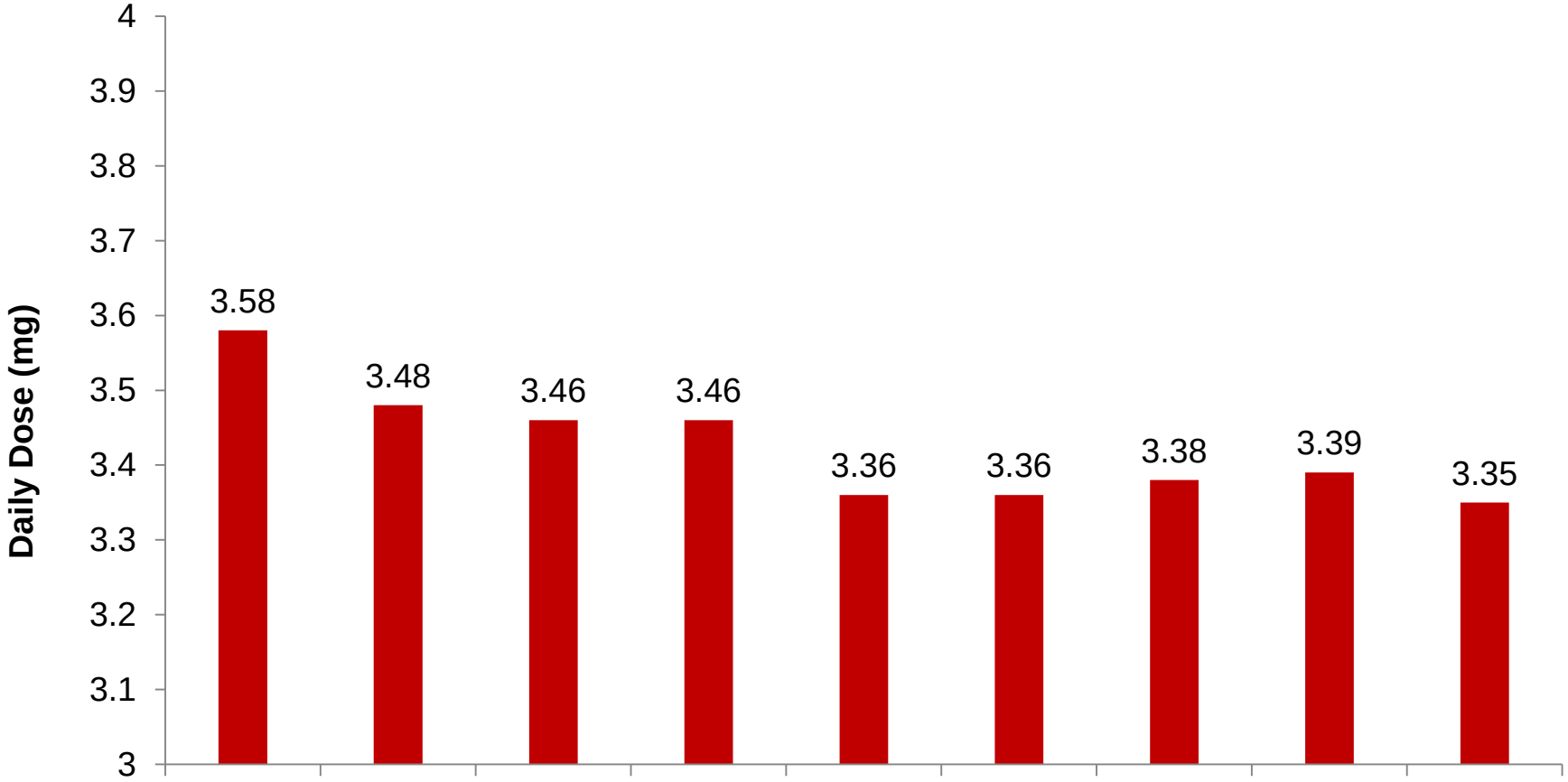
	Fruquintinib+BSC (N=278)	Placebo+BSC (N=138)
Median (months)	3.71	1.84
95% CI	3.65-4.63	1.81-1.84
Stratified HR (95% CI)	0.26 (0.21-0.34)	
p-value	<.001	

Table 1. Summary of Drug Exposure and Dose Modifications

	Fruquintinib+BSC (N=278)	Placebo+BSC (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 cycle		
Mean (SD)	5.5 (4.28)	2.2 (1.61)
Median (min-max)	4.0 (1-24)	2.0 (1-12)
Dose intensity, mg/day[a]		
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)
Patients with dose modification due to any TEAE, n (%)		
Dose reduction	67 (24.1)	6 (4.4)
Dose interruption	98 (35.3)	14 (10.2)

[a]Dose intensity (mg/day)=Cumulative dose (mg)/Total duration of exposure in day; the planned dose intensity was 3.75 mg/day

Figure 1. Mean Dose Intensity Over Time in Patients Treated With Fruquintinib



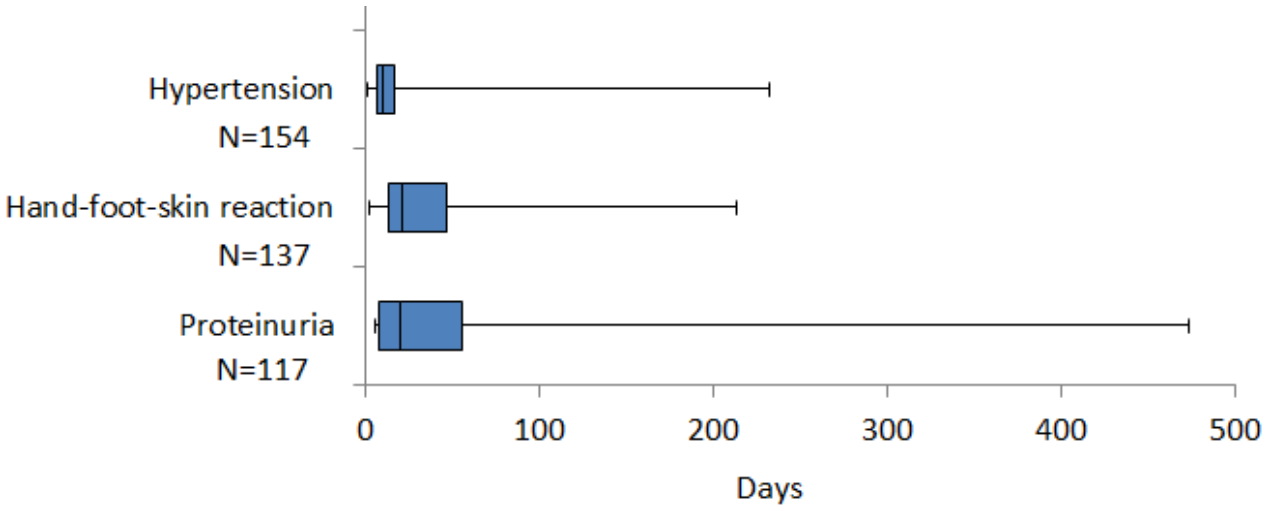
No. of patients treated with fruquintinib	278	255	183	164	132	115	80	70	50

Dose intensity (mg/day)=Cumulative dose (mg)/Total duration of exposure in day; the planned dose intensity was 3.75 mg/day

Table 2. Drug-Related AESI by Preferred Term (Occurring in ≥5% of Patients)

	Fruquintinib+BSC (N=278) n (%)			Placebo+BSC (N=137) n (%)		
AESI Category/ Preferred Term	**All Grades**	**Grades 3-4**	**Grade 5**	**All Grades**	**Grades 3-4**	**Grade 5**
Hypertension	165 (59.4)	64 (23.0)	0 (0.0)	23 (16.8)	3 (2.2)	0 (0.0)
Hypertension	154 (55.4)	59 (21.2)	0 (0.0)	21 (15.3)	3 (2.2)	0 (0.0)
Dermatological toxicity	154 (55.4)	31 (11.2)	0 (0.0)	7 (5.1)	0 (0.0)	0 (0.0)
Hand-foot-skin reaction	137 (49.3)	30 (10.8)	0 (0.0)	4 (2.9)	0 (0.0)	0 (0.0)
Rash	23 (8.3)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Proteinuria	144 (51.8)	12 (4.3)	0 (0.0)	39 (28.5)	0 (0.0)	0 (0.0)
Proteinuria	117 (42.1)	9 (3.2)	0 (0.0)	34 (24.8)	0 (0.0)	0 (0.0)
Protein urine present	30 (10.8)	3 (1.1)	0 (0.0)	6 (4.4)	0 (0.0)	0 (0.0)
Hemorrhage	98 (35.3)	1 (0.4)	1 (0.4)	22 (16.1)	0 (0.0)	0 (0.0)
Occult blood positive	33 (11.9)	0 (0.0)	0 (0.0)	7 (5.1)	0 (0.0)	0 (0.0)
Epistaxis	21 (7.6)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Hematuria	11 (4.0)	0 (0.0)	0 (0.0)	7 (5.1)	0 (0.0)	0 (0.0)
Blood urine present	14 (5.0)	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)
Thyroid dysfunction	54 (19.4)	0 (0.0)	0 (0.0)	8 (5.8)	0 (0.0)	0 (0.0)
Hypothyroidism	43 (15.5)	0 (0.0)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)

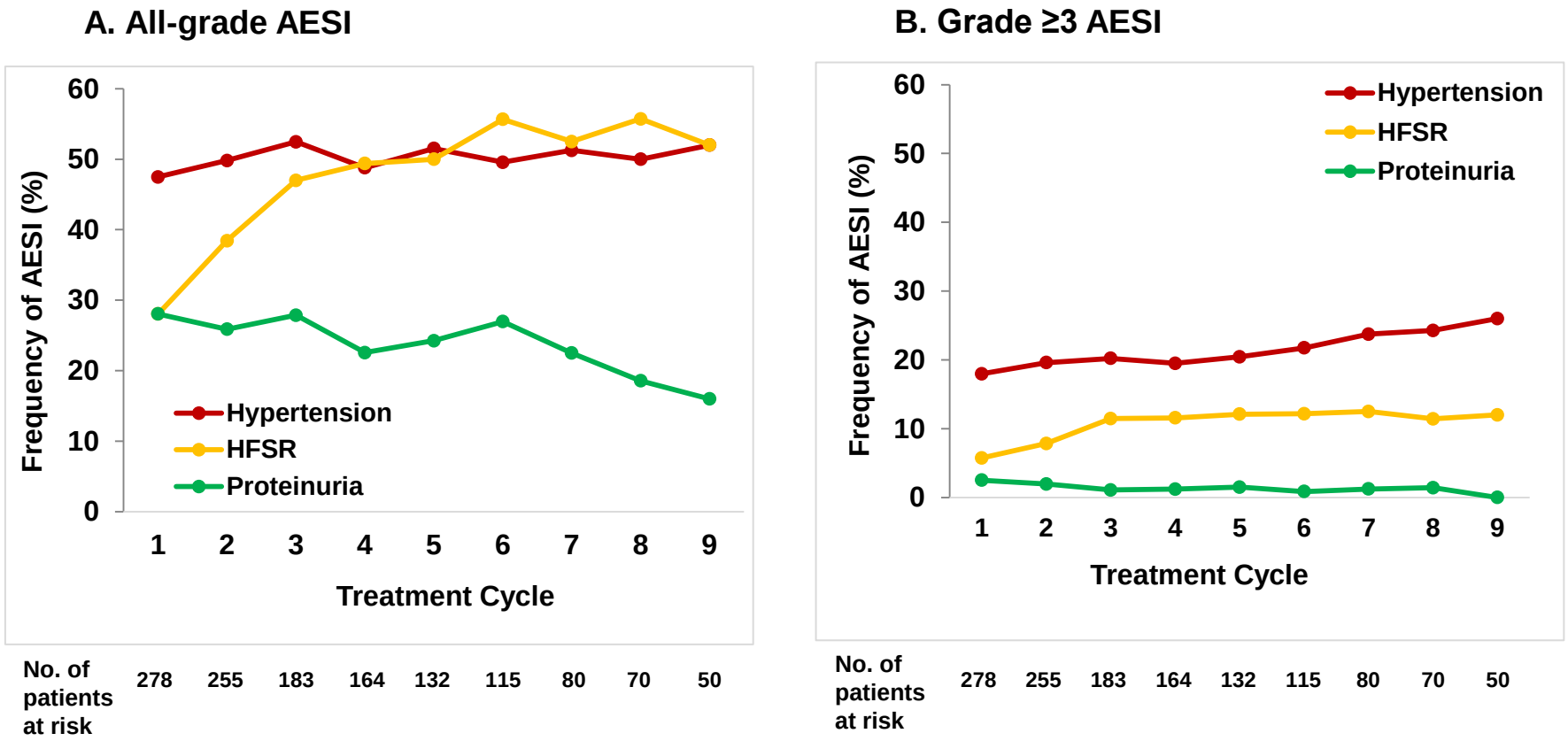
Figure 2. Time to First Occurrence of Specific AESI in Fruquintinib Group



	Min	Q1	Median	Q3	Max
Hypertension N=154	1	7	10	17	232
Hand-foot-skin reaction N=137	2	13	21	47	214
Proteinuria N=117	6	8	20	56	474

- The most common drug-related Grade ≥3 AESI (occurring in at least 3% of patients treated with fruquintinib) were hypertension (21.2%), hand-foot-skin reaction (10.8%), and proteinuria (3.2%)

Figure 3. Frequency of Specific AESI Over Time in Patients Treated With Fruquintinib



- Dose reduction due to hypertension occurred in 2.5% of patients, HFSR in 6.8%, and proteinuria in 4.3%
- Treatment discontinued due to hypertension in 0.4% of patients, HFSR in 0.4%, and proteinuria in 2.2%

Conclusion

- Fruquintinib was well tolerated in general
  - AESI were similar to those of same-class agents
  - AESI often occurred in the first few treatment cycles but do not appear to increase in frequency over time
- Most of these AESI can be clinically managed without discontinuing therapy

Back-Up Slides

Key Inclusion Criteria

- Histologically and/or cytologically diagnosed with mCRC (Stage IV)
- Had failed 2 prior treatments with fluropyrimidine, oxaliplatin, and irinotecan
- Prior anti-vascular endothelial growth factor (VEGF)- or anti-epidermal growth factor receptor (EGFR)-targeted therapy allowed but not mandatory
- Aged 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 informed consent

Table 3. Demographic and Patient Characteristics

	Fruquintinib+BSC (N=278) n (%)	Placebo+BSC (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 (Chinese)	272 (97.8)	135 (97.8)
Not Han (Chinese)	6 (2.2)	3 (2.2)
ECOG PS		
0	77 (27.7)	37 (26.8)
1	201 (72.3)	101 (73.2)

Table 4. Baseline Disease Characteristics

	Fruquintinib+BSC (N=278) n (%)	Placebo+BSC (N=138) n (%)
Primary site of the disease		
Colon	147 (52.9)	70 (50.7)
Rectal	125 (45.0)	60 (43.5)
Colorectal	6 (2.1)	7 (5.1)
Other[a]	0 (0.0)	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 anti-VEGF treatment		
Yes	84 (30.2)	41 (29.7)
No	194 (69.8)	97 (70.3)
Prior use of anti-EGFR treatment		
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)

[a]Ileocecal junction

Figure 4. Overall Survival

- FRESCO clearly succeeded in meeting the primary efficacy endpoint of overall survival

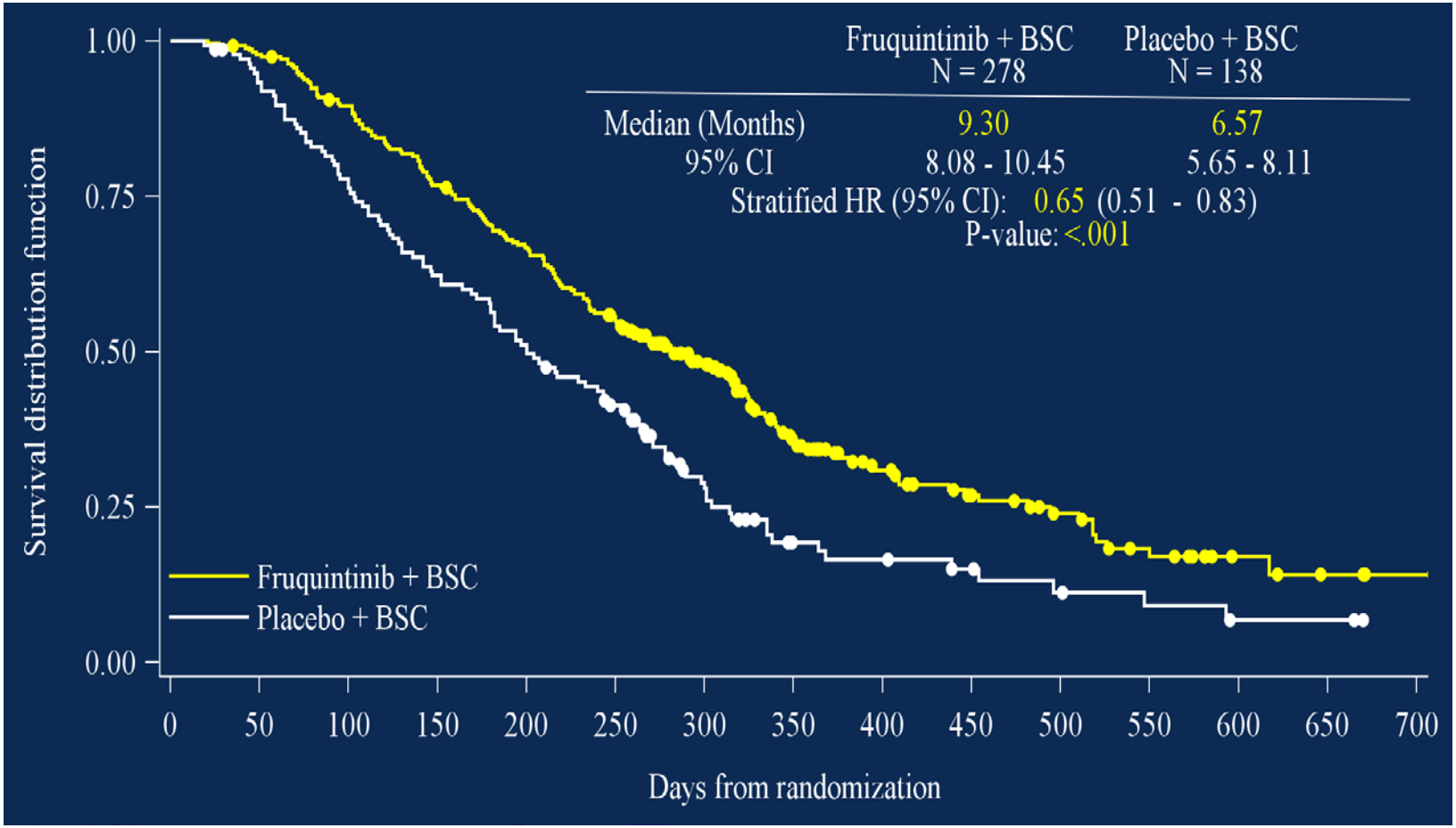


Figure 5. Progression-Free Survival

- Fruquinitinib significantly improves progression-free survival compared with placebo