Association Between Hand-Foot Skin Reaction (HFSR) and Survival Benefit of Fruquintinib in FRESCO Trial

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On Behalf of the FRESCO Investigators

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Disclosure

- Presenter: no conflicts of interest.
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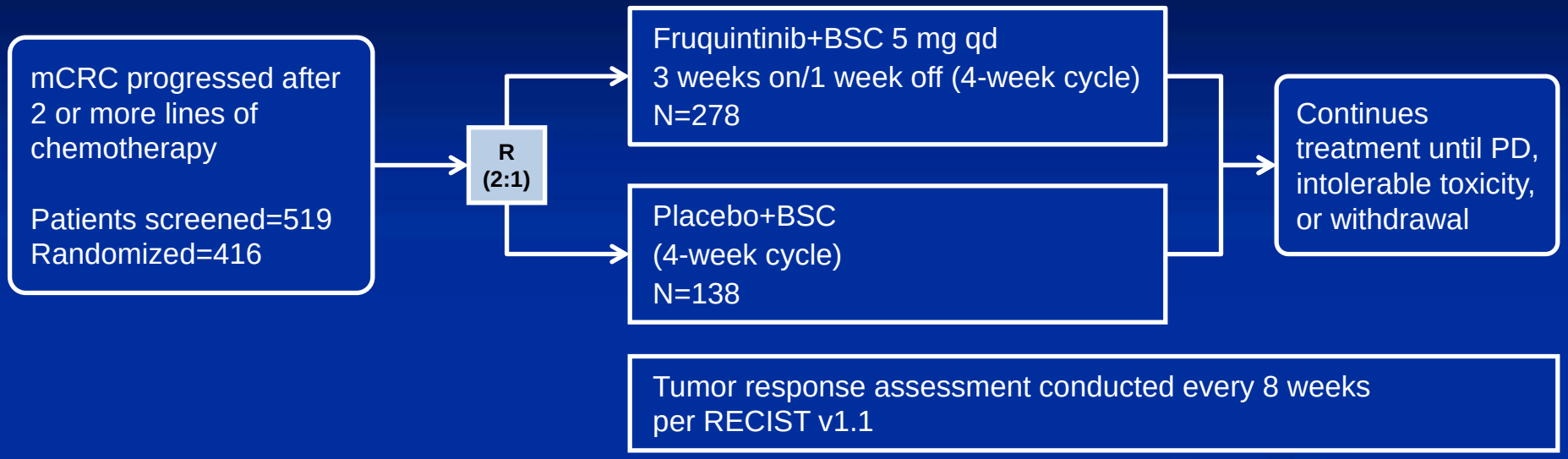
Background and Objective

- Fruquintinib is a highly selective and potent oral inhibitor of vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3[1].
- In the Phase III FRESCO trial (NCT02314819), fruquintinib demonstrated:
  - a statistically significant and clinically meaningful survival benefits in Chinese patients with mCRC.[2]
  - fruquintinib was well tolerated, and the safety profile was consistent with that of its class.[2]
- Hand-foot skin reaction (HFSR) was commonly reported as a drug-related adverse event (AE) in the fruquintinib group of FRESCO.
- This retrospective analysis explored whether HFSR in the fruquintinib group is associated with survival benefit.

1. *Zhou S, et al.Cancer Chemother Pharmacol.2017;80(3):563-573*
2. *Li J et al. JAMA. 2018;319:2486-96.*

Study Design

FRESCO Study Design



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	

1. Li J et al. JAMA. 2018 Jun 26;319(24):2486-2496.

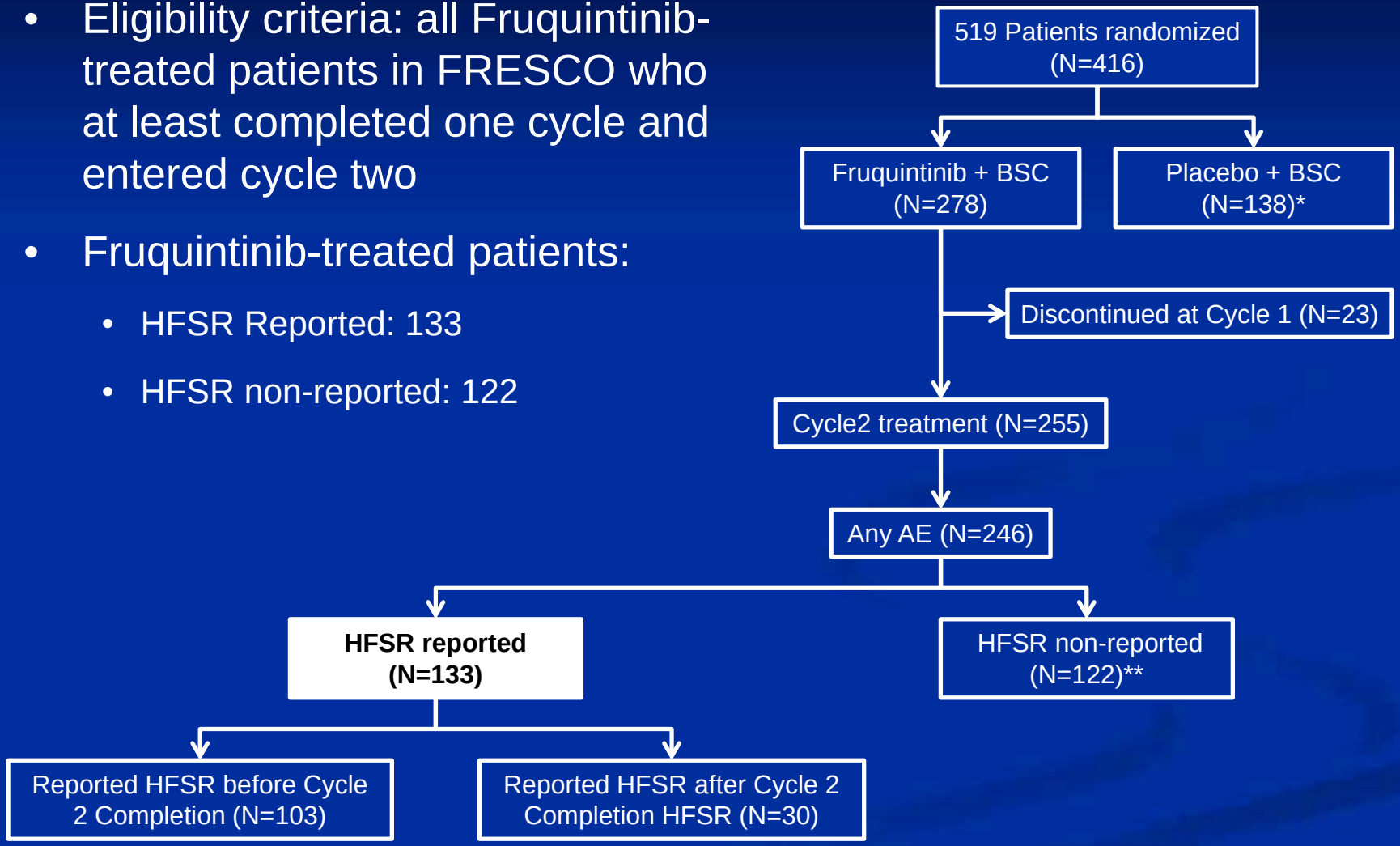
Methods

- This analysis used a subpopulation of the intent-to-treat population who completed at least one cycle and entered cycle two of fruquintinib treatment, to minimize lead time bias.
- The fruquintinib-treated patients were further divided into subgroups based on whether they reported HFSR.
- 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.

Results

Subject Disposition

- Eligibility criteria: all Fruquintinib-treated patients in FRESCO who at least completed one cycle and entered cycle two
- Fruquintinib-treated patients:
  - HFSR Reported: 133
  - HFSR non-reported: 122



* One patient did not take a dose, therefore the safety analysis set comprised data from 137 patients.

** HFSR non-reported group comprised 122 patients (113 patients who did not report HFSR and 9 patients who did not report any AE.

Incidence and Grade of HFSR (Safety Analysis Set)

Grade	Fruquintinib +BSC [1] (N=255) n (%)
Any Grade	133 (52.2)
Grade 1	57 (22.4)
Grade 2	47 (18.4)
Grade 3	29 (11.4)
Grade 4	0
Grade 5	0

1. Fruquintinib-treated patients that had entered the second cycle of treatment.

HFSR-Related Dosage Adjustment (Safety Analysis Set)

Adjustment	Fruquintinib +BSC [1] (N=255) n (%)
Permanently discontinued	1 (0.4)
Dose reduction	19 (7.5)
Dose discontinuation	17 (6.7)
Dose reduction or discontinuation	35 (13.7)
No dosage adjustment	95 (37.3)

1. Fruquintinib-treated patients that had entered the second cycle of treatment.

Drug Exposure for Fruquintinib-Treated Patients (Safety Analysis Set)

	HFSR reported		HFSR non-reported (N=122)
	(Any Grade) (N=133)	(≥ Grade 3) (N=29)	
Drug exposure, months			
Median (min-max)	5.5 (1.0-18.5)	5.5 (1.8-15.6)	3.1 (1.1-21.9)
Treatment cycle			
Median (min-max)	6.0 (2.0-20.0)	6.0 (2.0-17.0)	3.5 (2.0-24.0)
Dose intensity, mg/day [a]			
Median (min-max)	3.7 (1.7-4.2)	3.1 (2.2-3.8)	3.7 (1.5-4.3)
Relative dose intensity [b]			
Median (min-max)	1.0 (0.5-1.1)	0.8 (0.6-1.0)	1.0 (0.4-1.1)

Chart only includes data for fruquintinib-treated patients entered Cycle Two treatment

a. Dose intensity (mg/day) = Cumulative dose (mg) / Total duration of exposure in day

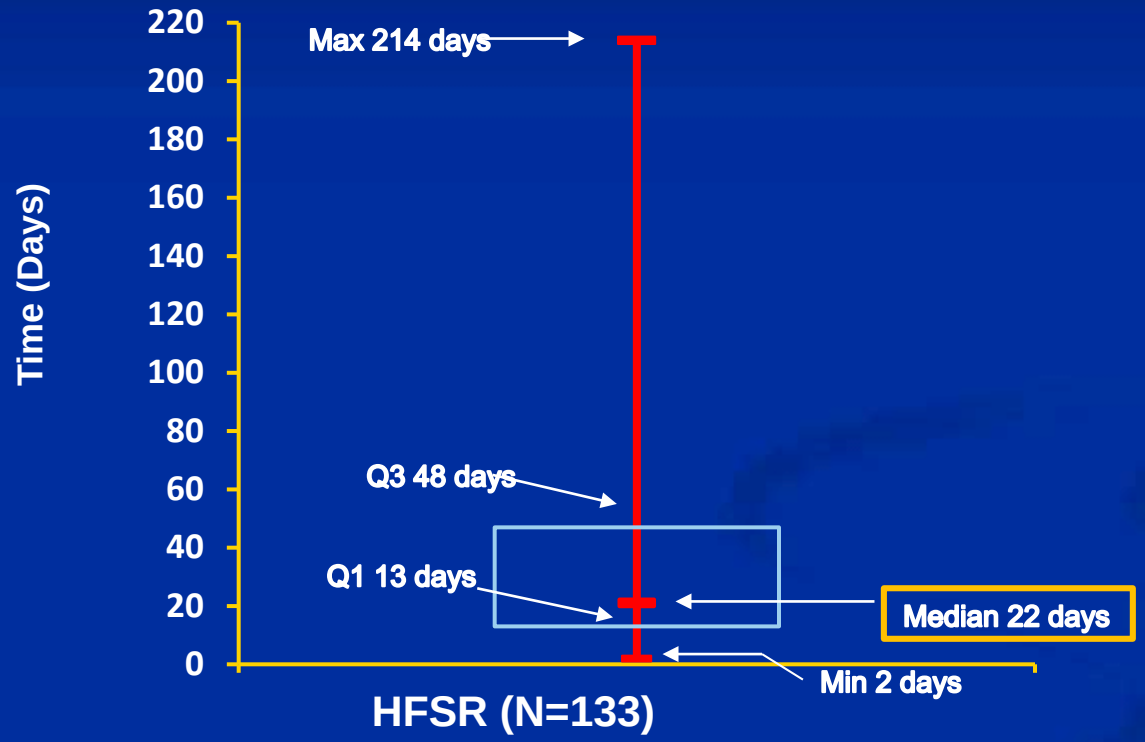
b. Relative dose intensity = Dose intensity / planned dose intensity; the planned dose intensity was 3.75 mg/day

Baseline Characteristics*

Patient Demographics / Baseline Characteristics		HFSR reported (N=133)	HFSR non-reported (N=122)
Age (years), Mean (SD)		54.4 (11.18)	54.3 (10.45)
Age, n (%)	< 65 years	104 (78.2)	105 (86.1)
	≥65 years	29 (21.8)	17 (13.9)
Sex, n (%)	Male / Female	81 (60.9) / 52 (39.1)	68 (55.7) / 54 (44.3)
ECOG, n (%)	0	38 (28.6)	36 (29.5)
	1	95 (71.4)	86 (70.5)
BMI (kg/m^2), mean (SD)		23.4 (3.14)	23.3 (3.24)
Ethnicity, n (%)	Han / Not Han	129 (97.0) / 4 (3.0)	120 (98.4) / 2 (1.6)
Stage, n (%)	Ⅰ	3 (2.3)	5 (4.1)
	Ⅱ	18 (13.5)	14 (11.5)
	Ⅲ	52 (39.1)	54 (44.3)
	Ⅳ	59 (44.4)	49 (40.2)
	Unknown	1 (0.8)	0
Primary site of the disease, n (%)	Colon	62 (46.6)	73 (59.8)
	Rectal	69 (51.9)	47 (38.5)
	Colorectal	2 (1.5)	2 (1.6)
Site(s) of metastasis, n (%)	Single / Multiple	7 (5.3) / 126 (94.7)	5 (4.1) / 117 (95.9)
Liver metastasis, n (%)	Yes	88 (66.2)	82 (67.2)
	No	45 (33.8)	40 (32.8)
K-Ras gene status, n (%)	Wild Type	74 (55.6)	69 (56.6)
	Mutant	59 (44.4)	53 (43.4)

* Intention-To-Treat (ITT) analysis

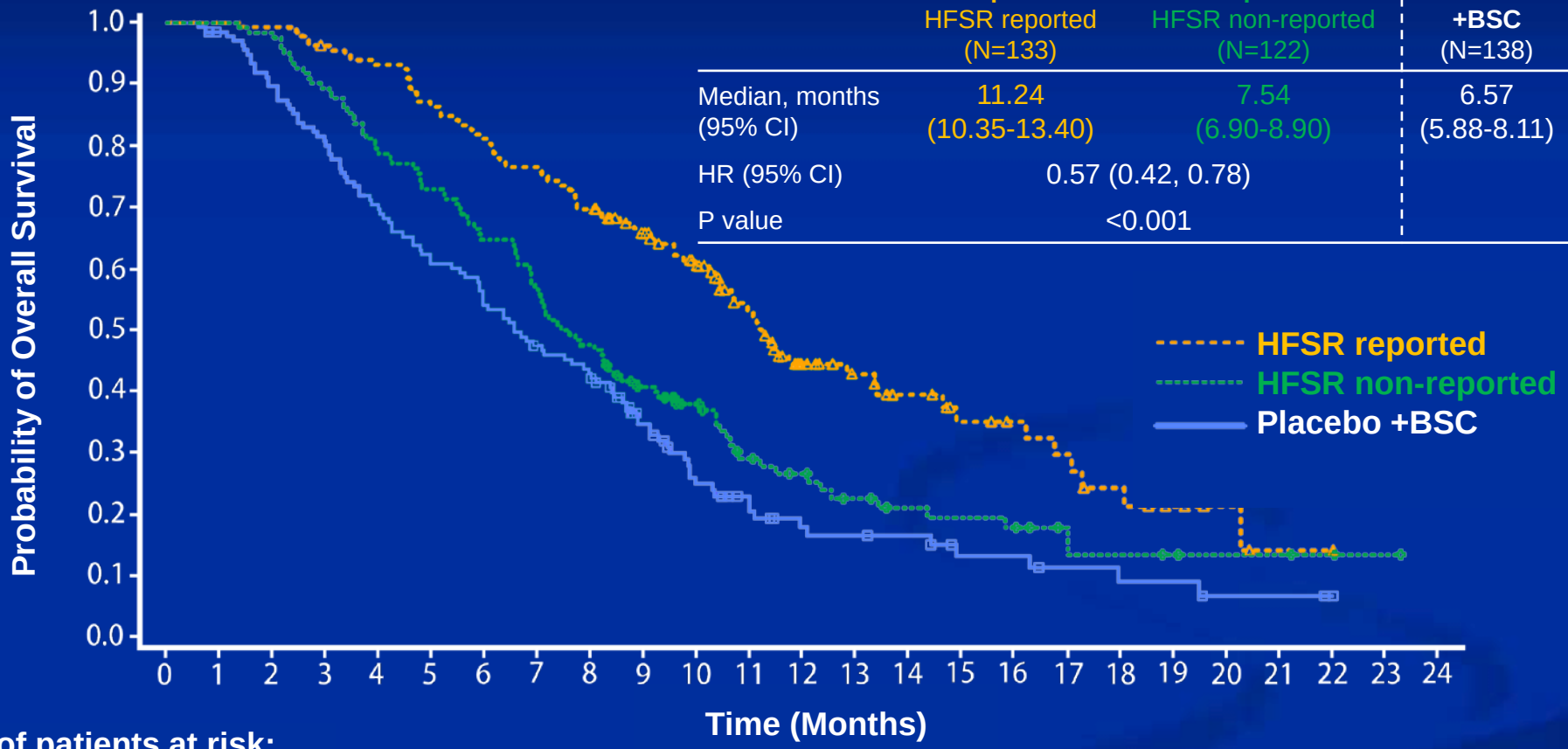
Fruquintinib-Treated Patients:* Time of First HFSR Report



* Intention-To-Treat (ITT) analysis

Overall Survival: Fruquintinib-Treated Patients Who Reported HFSR of Any Grade *

	Fruq. +BSC HFSR reported (N=133)	Fruq. +BSC HFSR non-reported (N=122)	Placebo +BSC (N=138)
Median, months (95% CI)	11.24 (10.35-13.40)	7.54 (6.90-8.90)	6.57 (5.88-8.11)
HR (95% CI)	0.57 (0.42, 0.78)		
P value	<0.001		



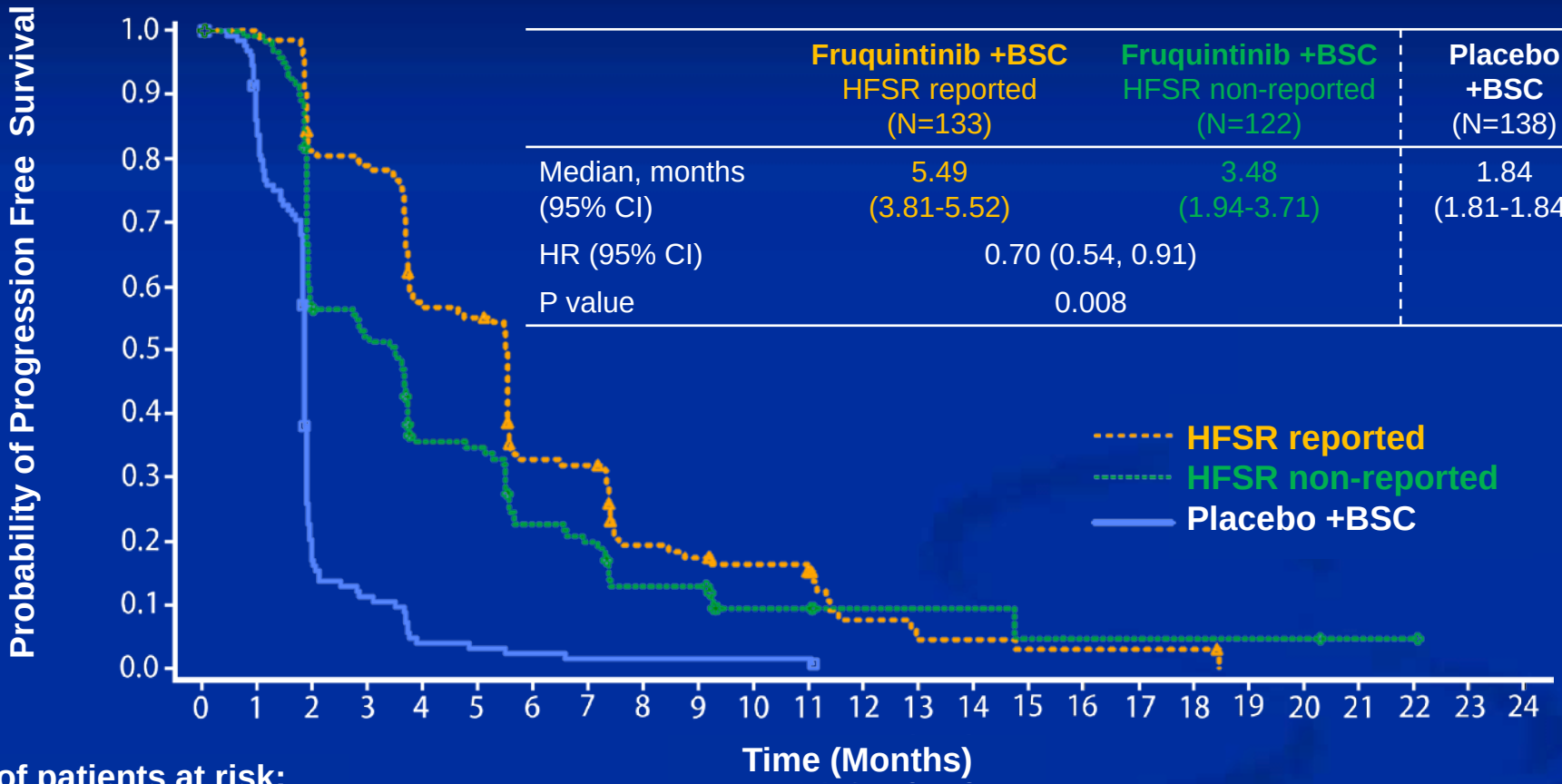
No. of patients at risk:

HFSR reported	133	133	132	127	123	114	107	101	92	79	66	50	33	26	20	15	13	11	8	5	3	1	1	0
HFSR non-reported	122	122	120	109	97	89	79	69	58	45	36	25	21	16	13	12	11	8	6	5	3	3	2	1	0
Placebo +BSC	138	133	121	109	95	82	73	63	57	38	25	19	13	12	11	7	7	5	4	4	2	2	1	0

* Intention-To-Treat (ITT) analysis

Progression-Free Survival (PFS): Patients Who Reported HFSR of Any Grade*

	Fruquintinib +BSC HFSR reported (N=133)	Fruquintinib +BSC HFSR non-reported (N=122)	Placebo +BSC (N=138)
Median, months (95% CI)	5.49 (3.81-5.52)	3.48 (1.94-3.71)	1.84 (1.81-1.84)
HR (95% CI)	0.70 (0.54, 0.91)		
P value	0.008		



No. of patients at risk:

HFSR reported	133	133	106	103	73	71	39	38	20	18	15	13	5	3	3	2	2	2	2	0			
HFSR non-reported	122	119	67	61	39	38	24	21	13	13	6	6	4	4	4	2	2	2	2	2	2	1	1	0
Placebo +BSC	138	107	21	14	5	4	3	2	2	2	2	2	0											

* Intention-To-Treat (ITT) analysis

Results Summary

- The median time-to-onset of HFSR (any grade) was 22 days for fruquintinib-treated patients.
- HFSR and dose of fruquintinib:
  - Most patients who had HFSR did not require dose reduction.
- Patients who had HFSR showed both OS and PFS benefits comparing with HFSR non-reported patients
  - Median OS: 11.24 vs. 7.54 months, HR=0.57; p<0.001
  - Median PFS: 5.49 vs. 3.48 months, HR=0.70; p=0.008

Conclusions

- The results of the subgroup analysis are consistent with the overall FRESCO results. Patients can benefit from fruquintinib treatment, compared to placebo.
- This post-hoc analysis further indicates that patients who had HFSR had a greater survival benefit from fruquintinib.
- Most HFSR reported are Grade 1-2. Most patients who had HFSR did not require dose reduction. In general, treatment with fruquintinib was well tolerated.