Efficacy and safety of fruquintinib in refractory metastatic colorectal cancer: A FRESCO-2 subgroup analysis by age

Poster 526P

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Background

- The risk of developing colorectal cancer (CRC) increases with age, with the majority of cases diagnosed in individuals over 50 years old[1,2]; however, the incidence of CRC is increasing among younger adults (<50 years) in the US and Europe[3,4]
- Fruquintinib is a highly selective oral inhibitor of vascular endothelial growth factor receptors (VEGFRs -1, -2, and -3)[5]
- Based on the results from the phase 3 FRESCO (NCT02314819) and FRESCO-2 studies (NCT04322539), fruquintinib was approved in the US and EU for patients with previously treated metastatic CRC (mCRC), regardless of biomarker status[6-9]
- In FRESCO-2, fruquintinib + best supportive care (BSC) versus placebo + BSC demonstrated significantly improved overall survival (OS; 7.4 vs 4.8 months; hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.55–0.80; p<0.001) and progression-free survival (PFS; 3.7 vs 1.8 months; HR 0.32, 95% CI 0.27–0.39; p<0.001), with a manageable safety profile consistent with the previously established monotherapy profile[7]
- We performed a subgroup analysis of FRESCO-2 to investigate efficacy and safety in patients with refractory mCRC by age (<55, 55−64, 65−74, and ≥75 years)

Methods

- The FRESCO-2 study design has been described in detail previously[7] (**Summary Panel**)
  - In this subgroup analysis, patients in FRESCO-2 were categorized according to the following age subgroups: <55, 55−64, 65−74 and ≥75 years
- Efficacy and safety were assessed according to age subgroups and by treatment arm
- OS (primary endpoint) and PFS were evaluated by the Kaplan–Meier method with differences tested using the log-rank test; survival HRs were estimated using a Cox proportional hazards model
- Time to deterioration (TTD) of Eastern Cooperative Oncology Group performance status (ECOG PS) was investigated via Kaplan–Meier analysis of time from randomization to first occurrence of ECOG PS ≥2 or death within safety follow up (30 +/-7 days after end of treatment)
- Treatment emergent adverse events (TEAEs) were coded according to MedDRA (version 25.0) and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0)

Results

Patients

- Of the 691 patients from FRESCO-2, 461 and 230 patients were randomized to fruquintinib and placebo, respectively, with a median age of 64 years in both treatment arms[7]
- Baseline characteristics were generally similar between treatment arms across age subgroups (**Table 1**)

Table 1. Baseline characteristics in the fruquintinib and placebo arms according to age subgroups (ITT population)

	<55 years (n=147)		55–64 years (n=219)		65–74 years (n=266)		≥75 years (n=59)	
	Fruquintinib (n=103)	Placebo (n=44)	Fruquintinib (n=144)	Placebo (n=75)	Fruquintinib (n=170)	Placebo (n=96)	Fruquintinib (n=44)	Placebo (n=15)
Median age, years (range)	48 (25–54)	49 (30–54)	60 (55–64)	61 (55–64)	69 (65–74)	68 (65–74)	77 (75–82)	77 (75–86)
Male, %	47.6	56.8	56.9	60.0	50.6	58.3	63.6	93.3
ECOG PS, %								
0	45.6	52.3	52.1	44.0	36.5	43.8	27.3	26.7
1	54.4	47.7	47.9	56.0	63.5	56.3	72.7	73.3
Primary site at first diagnosis*, %								
Colon	56.3	52.3	54.9	50.7	64.7	67.7	72.7	73.3
Rectum	31.1	43.2	38.9	34.7	27.6	22.9	18.2	20.0
Number of prior treatment lines for metastatic disease, median (range)	4.0 (2.0–11.0)	4.0 (2.0–10.0)	4.0 (2.0–16.0)	4.0 (2.0–12.0)	4.0 (2.0–11.0)	5.0 (2.0–11.0)	4.5 (2.0–9.0)	4.0 (2.0–11.0)
≤3, %	23.3	31.8	27.8	30.7	29.4	22.9	25.0	33.3
>3, %	76.7	68.2	72.2	69.3	70.6	77.1	75.0	66.7
Liver metastases, %	73.8	70.5	75.0	68.0	72.9	64.6	70.5	80.0
Median duration of metastatic disease, months (range)	35.1 (11.4–105.2)	38.8 (7.1–105.3)	38.7 (6.0–122.9)	39.6 (8.9–147.1)	38.4 (9.3–192.8)	45.3 (15.6–117.0)	50.7 (16.5–128.0)	36.3 (12.4–106.1)
>18 months, %	93.2	90.9	88.9	93.3	92.9	96.9	95.5	93.3
≤18 months, %	6.8	9.1	11.1	6.7	7.1	3.1	4.5	6.7
RAS mutation-positive, %	58.3	59.1	61.8	72.0	68.8	57.3	56.8	66.7
Prior VEGF inhibitor, %	100 (97.1)	43 (97.7)	140 (97.2)	74 (98.7)	165 (97.1)	91 (94.8)	40 (90.9)	13 (86.7)
Prior EGFR inhibitor, %	47 (45.6)	18 (40.9)	60 (41.7)	24 (32.0)	56 (32.9)	42 (43.8)	17 (38.6)	4 (26.7)

*Remaining percentage for primary site at first diagnosis = colon and rectum

Question

What are the efficacy and safety outcomes of fruquintinib + BSC versus placebo + BSC in patients with refractory mCRC aged <55, 55−64, 65−74, and ≥75 years?

Methods

FRESCO-2

Patients with mCRC from North America, Europe, Japan, and Australia (**N=691**)

R 2:1

Fruquintinib (n=461)
5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

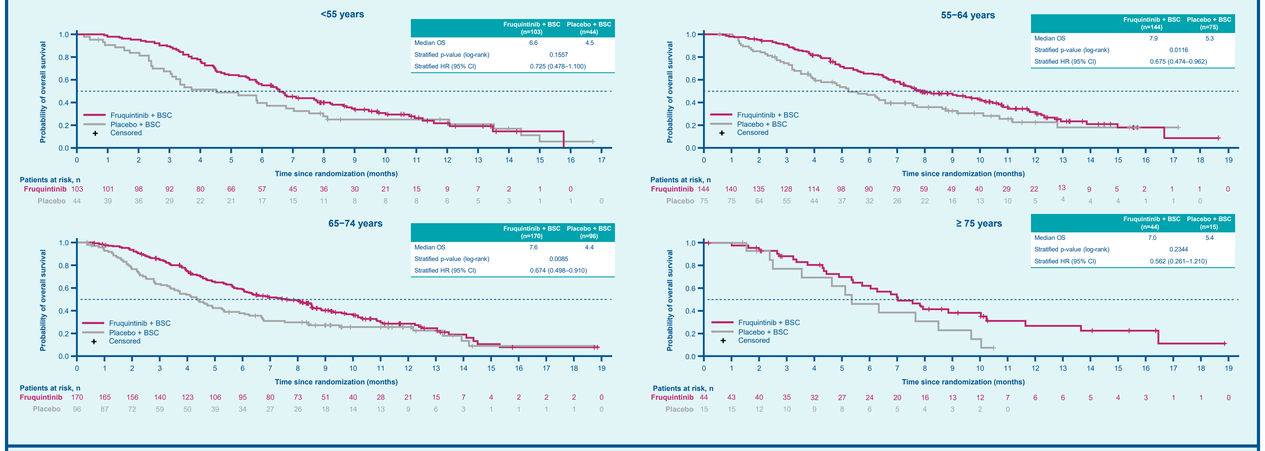
Placebo (n=230)
5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

Treatment until PD or unacceptable toxicity

Subgroup analysis for efficacy and safety by age
- **<55 years** (n=147)
- **55–64 years** (n=219)
- **65–74 years** (n=266)
- **≥ 75 years** (n=59)

Primary endpoint: OS
Secondary endpoints: PFS, safety
Post-hoc: ECOG PS deterioration

Figure 1. Kaplan-Meier plot of OS with fruquintinib versus placebo according to age subgroups (ITT population)



Key conclusions

Fruquintinib provides an effective and tolerable treatment option for patients with previously treated mCRC, irrespective of age

Time to event endpoints

- Fruquintinib prolonged OS (**Figure 1, Summary Panel**), and PFS (**Figure 2**) compared with placebo across all age subgroups; fruquintinib also delayed deterioration to ECOG PS ≥2 or death within safety follow up (30 +/-7 days after the end of treatment) compared with placebo across all age subgroups; however, the difference in median was small in the subgroup of patients aged ≥75 (**Figure 3**)

Figure 2. Forest plot of PFS in the fruquintinib and placebo arms according to age subgroups (ITT population)

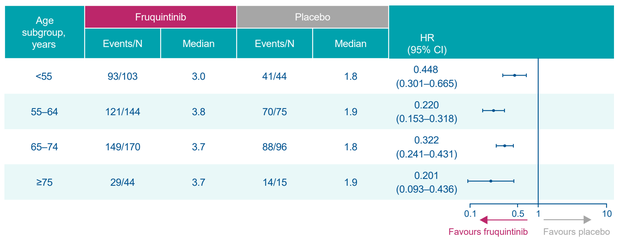
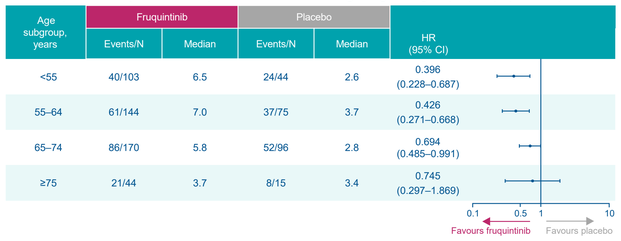


Figure 3. Forest plot of TTD to ECOG PS ≥2 or death within safety follow up (30 +/-7 days after end of treatment) in the fruquintinib and placebo arms according to age subgroups (ITT population)



Safety

- Rates of TEAEs with fruquintinib were generally similar across age subgroups (**Table 2**)
- The most frequently reported grade ≥3 TEAE with fruquintinib was hypertension for patients aged <55 (13.7%), 55−64 (14.8%), and 65−74 (12.4%), and palmar-plantar erythrodysesthesia (PPE) for patients aged ≥75 years (16.3%) (**Table 3**)

Table 2. Overall safety summary of fruquintinib and placebo according to age subgroups (safety population*)

Patients, n (%) unless stated	<55 years (n=144)		55–64 years (n=218)		65–74 years (n=266)		≥75 years (n=58)	
	Fruquintinib (n=102)	Placebo (n=42)	Fruquintinib (n=142)	Placebo (n=76)	Fruquintinib (n=169)	Placebo (n=97)	Fruquintinib (n=43)	Placebo (n=15)
Treatment cycles received, median (Q1, Q3)	3.0 (2.0–6.0)	2.0 (1.0–2.0)	4.0 (2.0–7.0)	2.0 (2.0–3.0)	3.0 (2.0–6.0)	2.0 (1.0–3.0)	3.0 (2.0–5.0)	2.0 (1.0–3.0)
Any TEAE	100 (98.0)	41 (97.6)	140 (98.6)	67 (88.2)	168 (99.4)	92 (94.8)	43 (100)	13 (86.7)
Grade ≥3	63 (61.8)	22 (52.4)	90 (63.4)	31 (40.8)	102 (60.4)	57 (58.8)	31 (72.1)	6 (40.0)
Treatment-related	87 (85.3)	20 (47.6)	125 (88.0)	42 (55.3)	144 (85.2)	58 (59.8)	39 (90.7)	10 (66.7)
Grade ≥3 treatment-related	32 (31.4)	4 (9.5)	56 (39.4)	5 (6.6)	56 (33.1)	16 (16.5)	20 (46.5)	1 (6.7)
Leading to dose reduction	19 (18.6)	1 (2.4)	38 (26.8)	4 (5.3)	38 (22.5)	4 (4.1)	15 (34.9)	0
Leading to dose interruption	49 (48.0)	10 (23.8)	59 (41.5)	19 (25.0)	83 (49.1)	30 (30.9)	22 (51.2)	2 (13.3)
Leading to discontinuation	19 (18.6)	10 (23.8)	25 (17.6)	14 (18.4)	37 (21.9)	21 (21.6)	12 (27.9)	4 (26.7)
Leading to death†	14 (13.7)	6 (14.3)	12 (8.5)	14 (18.4)	17 (10.1)	22 (22.7)	5 (11.6)	3 (20.0)

*Of 5 patients assigned to the fruquintinib arm, 3 did not receive fruquintinib treatment and 2 received placebo instead; 2 patients assigned to the placebo arm did not receive treatment. †Only 2 deaths were deemed treatment-related in the 55–64-year age subgroup: 1 due to intestinal perforation in the fruquintinib arm and 1 due to cardiac arrest in the placebo group.

Table 3. Grade ≥3 TEAEs occurring in ≥4% of patients in the fruquintinib arm according to age subgroups (safety population*)

Preferred term, n (%)	<55 years (n=144)		55–64 years (n=218)		65–74 years (n=266)		≥75 years (n=58)	
	Fruquintinib (n=102)	Placebo (n=42)	Fruquintinib (n=142)	Placebo (n=76)	Fruquintinib (n=169)	Placebo (n=97)	Fruquintinib (n=43)	Placebo (n=15)
Hypertension	14 (13.7)	0	21 (14.8)	0	21 (12.4)	2 (2.1)	6 (14.0)	0
Disease progression	7 (6.9)	3 (7.1)	7 (4.9)	10 (13.2)	11 (6.5)	14 (14.4)	2 (4.7)	1 (6.7)
PPE	6 (5.9)	0	9 (6.3)	0	7 (4.1)	0	7 (16.3)	0
Abdominal pain	5 (4.9)	1 (2.4)	4 (2.8)	3 (3.9)	3 (1.8)	3 (3.1)	2 (4.7)	0
Asthenia	4 (3.9)	1 (2.4)	10 (7.0)	4 (5.3)	17 (10.1)	3 (3.1)	4 (9.3)	1 (6.7)
Back pain	4 (3.9)	1 (2.4)	1 (0.7)	0	1 (0.6)	2 (2.1)	0	0
Pneumonia	4 (3.9)	0	2 (1.4)	1 (1.3)	2 (1.2)	0	2 (4.7)	0
ALT increased	3 (2.9)	1 (2.4)	3 (2.1)	0	8 (4.7)	0	0	0
Fatigue	2 (2.0)	1 (2.4)	7 (4.9)	1 (1.3)	7 (4.1)	0	2 (4.7)	0
General physical deterioration	0	0	6 (4.2)	0	4 (2.4)	4 (4.1)	1 (2.3)	1 (6.7)

*Of 5 patients assigned to the fruquintinib arm, 3 did not receive fruquintinib treatment and 2 patients received placebo instead; 2 patients assigned to placebo did not receive treatment. ALT, alanine aminotransferase

Conclusions

- Consistent with the overall FRESCO-2 population, OS and PFS were longer with fruquintinib compared with placebo in all age subgroups, including in young onset and elderly patients with refractory mCRC
- Fruquintinib has a safety profile that is manageable, and consistent with the established profile for fruquintinib monotherapy across all age subgroups
- Fruquintinib provides an effective and tolerable treatment option for patients with previously treated mCRC irrespective of age

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Acknowledgments

This study was funded by HUTCHMED. The authors would like to thank all patients and their families, as well as all investigators for their valuable contributions to this study. Medical writing support for the development of this poster, under the direction of the authors, was provided by Reshme Govender, PhD, of Ashfield MedComms, an Inizio Company, funded by Takeda Pharmaceuticals U.S.A., Inc., Lexington, MA, and complied with the Good Publication Practice (GPP) guidelines (DeTora LM, et al. *Ann Intern Med*. 2022;175:1298–304).

Disclosures

EE: Honoraria from Amgen, Bayer, Hoffman-La Roche, Merck Serono, MSD, Novartis, Organon, Pfizer, Pierre Fabre, Sanofi, Seagen, Servier, and Takeda; Grants and/or funds from Amgen Inc, Array Biopharma Inc, AstraZeneca Pharmaceuticals LP, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Debiopharm International SA, Genentech Inc, HalioDX SAS, Hoffmann-La Roche Ltd, Hutchison MediPharma International, Janssen-Cilag SA, MedImmune, Menarini, Merck Health KGAA, Merck Sharp & Dohme, Merus NV, Mirati, Novartis Farmacéutica SA, Pfizer, Pharma Mar, Sanofi Aventis Recherche & Développement, Servier, and Taiho Pharma USA Inc.; Non-financial conflicts with American Society of Clinical Oncology (ASCO) as a volunteer member of the ASCO Annual Meeting Scientific Program Committee: Developmental Therapeutics – Immunotherapy, European Society for Medical Oncology (ESMO) as speaker for the ESMO Academy; Sociedad Española de Oncología Médica (SEOM) as coordinator of the SEOM +MIR Section of Residents and Young Assistants

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Presented at ESMO Congress, 13–17 September 2024, Barcelona, Spain. For questions or comments, please contact Dr Elena Elez: meelez@vhio.net