Real-world effectiveness and safety of fruquintinib in patients with metastatic colorectal cancer in Spain: the FrESP study

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BACKGROUND

- Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide and the most commonly diagnosed cancer in Spain. Metastatic CRC (mCRC) remains associated with poor outcomes, with a 5-year survival rate of ~17%[1-3]
- Fruquintinib is a highly selective oral inhibitor of vascular endothelial growth factor receptors (VEGFRs) 1-3[4]
- Based on the results from the phase III FRESCO (NCT02314819) and FRESCO-2 (NCT04322539) trials, fruquintinib was globally approved for refractory mCRC[5-7]
- In FRESCO-2, fruquintinib plus best supportive care improved overall survival (OS; 7.4 *vs.* 4.8 months, HR 0.66) and progression-free survival (PFS; 3.7 *vs.* 1.8 months, HR 0.32), with a favorable safety profile[6]
- Real-world evidence (RWE) in European populations remains limited

OBJECTIVE

- To evaluate the real-world effectiveness, safety, and tolerability of fruquintinib in previously treated mCRC in Spain through the Named Patient Program (NPP), following the publication of the first FRESCO-2 results

METHODS

- **Design**: Retrospective, multicenter, non-interventional RWE cohort study across 40 Spanish oncology centers
- **Population**: Adult patients with mCRC who had received previous systemic treatment and received ≥1 fruquintinib cycle under the NPP*; treatment initiation dates ranged from January to December 2024. (*NPP inclusion criteria: Adult patients who progressed on, or were intolerant to, fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy and VEGF/EGFR inhibitors, as indicated. Patients had received TAS-102 and regorafenib unless intolerant or not locally available)
- **Treatment**: Fruquintinib was administered orally following the standard clinical practice of each hospital (5 mg once daily on days 1-21 in 28-day cycles)
- **Data collection**: Demographic, clinical, molecular, treatment, and outcome data were retrospectively collected from electronic medical records, oncology, pathology, radiology, and pharmacy records using a pseudonymized electronic case report form up to the last patient last visit (10 January 2026); database lock occurred on 24 March 2026 following data monitoring and query resolution
- **Endpoints**: Primary endpoints were OS and PFS estimated by Kaplan–Meier (95% confidence interval [CI]); survival HRs were estimated using a Cox proportional hazards model. Secondary endpoints included overall response rate (ORR), disease control rate (DCR), and grade ≥3 treatment-emergent adverse events (TEAEs), graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0)
- Efficacy and safety analyses were performed in the Full Analysis Set (FAS, N=91)
- **Exploratory subgroup analysis**: Exploratory/post-hoc-adapted subgroup analyses by best (BPC), good (GPC), and poor (PPC) prognostic class (adapted from Tabernero *et al.*, ESMO Open 2020[8]) were performed

RESULTS

Patients

- 91 of the 102 patients screened met the eligibility criteria and were included in the FAS
- The median study follow-up time was 6.7 (range 0.7-23.8) months
- Baseline characteristics of the FAS population are shown in **Table 1**
- Median age was 64.3 years; 53.9% were male; ECOG 0–1 in 98.6%; 74.7% had liver metastases; 98.8% were MSS/pMMR stable and 64.7% harbored KRAS mutations; median 5 prior lines of therapy (range 3-17), and median treatment duration 2.1 months (range 0.7-9.7)

Table 1. Baseline characteristics

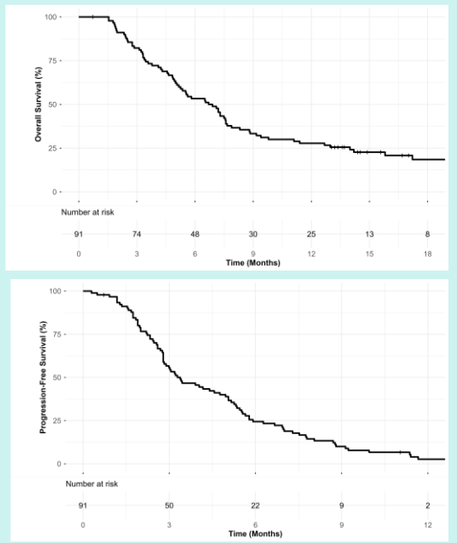
Characteristics	FAS (N=91)
Median age, years (range)	64.3 (38.7-86.7)
Age group, n (%)	
≤70 years	67 (73.6)
≤80 years	86 (94.5)
Male, n (%)	49 (53.9)
ECOG PS at C1D1 [a], n (%)	
0-1	73 (98.6)
≥2	1 (1.4)
Primary tumor laterality, n (%)	
Left (including rectum)	66 (72.5)
Right (including transverse)	17 (18.7)
Multicentric	8 (8.8)
Site of metastases[b], n (%)	
Liver	68 (74.7)
Lung	57 (62.6)
Distant lymph node	27 (29.7)
Peritoneum	17 (18.9)
Median number of metastatic sites[b]	2.0 (1.0-5.0)
Prognostic subgroup[c], n (%)	
BPC	10 (11.0)
GPC	3 (3.3)
PPC	78 (85.7)
MS-MMR[d], n (%)	
MSS/pMMR (stable)	79 (98.8)
MSI/dMMR (unstable)	1 (1.3)
KRAS mutation-positive[e], n (%)	55 (64.7)
NRAS mutation-positive[f], n (%)	6 (9.8)
BRAF mutation-positive[g], n (%)	4 (6.8)
Number of prior systemic therapy lines, median (range)	5.0 (3.0-17.0)
=3, n (%)	22 (24.2)
>3, n (%)	69 (75.8)
Median fruquintinib treatment duration, months (range)	2.1 (0.7-9.7)

[a]n=74; [b]n=90; [c]Prognostic subgroups were defined according to metastatic burden, timing, and hepatic involvement. Patients with <3 metastatic sites, ≥18 months from initial colorectal cancer diagnosis to metastatic disease diagnosis, and no liver metastases were classified as BPC; patients with <3 metastatic sites, ≥18 months, and liver metastases were classified as GPC; all remaining patients were classified as PPC; [d]n=80 [e]n=85, [f]n=61, [g]n=59.
C1D1, Cycle 1 Day 1; BPC, best prognostic class; CRC, colorectal cancer; dMMR, deficient mismatch repair; GPC, good prognostic class; MSI, microsatellite instability; MSS, microsatellite stable; pMMR, proficient mismatch repair; PPC, poor prognostic class.

Effectiveness

- Median OS was 6.8 months (95% CI: 5.3-7.7) (**Figure 1A**)
  - 3-month OS rate: 82.2% (95% CI: 74.7-90.5%)
  - 6-month OS rate: 53.3% (95% CI: 44.0-64.7%)
  - 12-month OS rate: 27.8% (95% CI: 19.9-38.8%)
- Median PFS was 3.4 months (95% CI: 2.8-4.8) (**Figure 1B**)
  - 3-month PFS rate: 55.6% (95% CI: 44.7-65.1%)
  - 6-month PFS rate: 24.5% (95% CI: 16.2-33.7%)
  - 12-month PFS rate: 2.7% (95% CI: 0.5-8.1%)

Figure 1. Kaplan-Meier curves of (**A**) OS and (**B**) PFS



CI, confidence interval; FAS, Full Analysis Set; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival.

Secondary efficacy outcomes

- Among patients with evaluable tumor response (n=77), PD was the most frequent BOR (43/77, 55.8%), followed by SD (26/77, 33.8%) and PR (4/77, 5.2%); no CR was observed (**Table 2**)
- In the FAS (N=91), ORR was 4.4% (95% CI, 1.7-10.8) and DCR was 33.0% (95% CI, 24.2-43.1)

Table 2. Tumor response outcomes

n (%)	FAS (N=91)
BOR[a]	
CR	0 (0)
PR	4 (5.2)
SD	26 (33.8)
PD	43 (55.8)
Indeterminate	4 (5.2)
ORR (CR+PR)[b]	4 (4.4)
[95% CI]	[1.7-10.8]
DCR[c]	30 (33.0)
[95% CI]	[24.2-43.1]

[a]n=77. [b]ORR is the percentage of patients who achieved CR or PR as the best overall response. [c]DCR is the percentage of patients who achieved CR, PR, or SD as the best overall response.
BOR, best overall response; CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

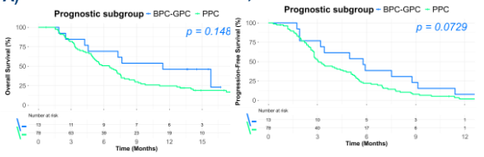
Safety

- TEAEs occurred in 60/91 patients (65.9%); 55 patients (60.4%) experienced fruquintinib-related TEAEs as per investigator assessment (**Table 3**)
- Grade 3-5 TEAEs occurred in 37 patients (40.7%); 28 patients (30.8%) had fruquintinib-related Grade ≥3 TEAEs
- TEAEs led to permanent discontinuation, dose reduction, and dose interruption in 16 (17.6%), 31 (34.1%), and 45 (49.5%) patients, respectively. Four patients (4.4%) experienced a TEAE resulting in death, including one (1.1%) considered fruquintinib-related (G3 gastrointestinal perforation and peritonitis) and three (3.3%) as not related (G5 intestinal obstruction, G4 craniocerebral injury, G5 tumor perforation)
- **Table 4** shows the most common grade ≥3 TEAEs, including grade ≥3 fruquintinib-related TEAEs

Exploratory subgroup analysis

- In the (BPC+GPC) *vs.* PPC subgroup analysis (n=13 *vs.* n=78), median OS was 11.4 and 6.5 months, respectively (HR 1.72; 95% CI 0.82–3.61), and median PFS was 5.8 and 3.1 months, respectively (HR 1.76; 95% CI 0.95-3.26) (**Figure 2**)

Figure 2. Kaplan-Meier curves of (**A**) OS and (**B**) PFS by prognostic subgroup



These exploratory results must be interpreted cautiously because of the small subgroup sizes, the heterogeneity in the number of prior lines received, and the descriptive, non-comparative nature of the analyses.
BPC, best prognostic class; GPC, good prognostic class; OS, overall survival; PFS, progression-free survival; PPC, poor prognostic class.

Table 3. Overall safety summary of fruquintinib

Patients, n (%)	FAS (N=91)
AEs[a]	60 (65.9)
TEAEs	60 (65.9)
Unrelated	20 (22.0)
Fruquintinib-related	55 (60.4)
Serious TEAEs	34 (37.4)
Unrelated	13 (14.3)
Fruquintinib-related	24 (26.4)
Grade 3–5 TEAEs	37 (40.7)
Unrelated	13 (14.3)
Fruquintinib-related	28 (30.8)
TEAE – Fruquintinib permanent discontinuation	16 (17.6)
Unrelated	5 (5.5)
Fruquintinib-related	12 (13.2)
TEAE – Fruquintinib dose reduction	31 (34.1)
Unrelated	1 (1.1)
Fruquintinib-related	31 (34.1)
TEAE – Fruquintinib dose interruption	45 (49.5)
Unrelated	14 (15.4)
Fruquintinib-related	40 (44.0)
TEAE resulting in death	4 (4.4)
Unrelated	3 (3.3)
Fruquintinib-related	1 (1.1)

[a]Non-exclusive categories. AE, adverse event; TEAE, treatment-emergent adverse event.

Table 4. Most frequent grade ≥3 TEAEs and fruquintinib-related TEAEs

Grade ≥3	n (%)	
	TEAEs	Fruquintinib-related TEAEs
Asthenia/Fatigue	13 (14.3)	12 (13.2)
Hypertension	5 (5.5)	4 (4.4)
Anemia	3 (3.3)	2 (2.2)
Diarrhea	3 (3.3)	3 (3.3)
Hepatic toxicity	3 (3.3)	3 (3.3)
Decreased appetite	3 (3.3)	2 (2.2)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Fruquintinib demonstrated effectiveness and a manageable safety profile in a real-world Spanish mCRC population, consistent with FRESCO-2 results. Most of them had prior exposure to TAS-102 and regorafenib by the NPP inclusion criteria
- A trend towards better outcomes was descriptively observed in BPC+GPC *vs.* PPC patients
- These findings provide complementary real-world evidence supporting fruquintinib as a treatment option for patients with refractory mCRC in Spain

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Disclosures

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