Quality of Life Impact of Adverse Events Associated With Systemic Therapies for Metastatic Colorectal Cancer Previously Treated With Standard Therapies and Biologics Across 13 Countries in Europe, North America, and Asia

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Summary Panel

Question: How do grade ≥3 AEs impact the QoL of patients from 13 countries in Europe, North America, and Asia with previously treated mCRC receiving either fruquintinib, T/T, T/T + bev, or regorafenib?

Methods

Grade 3/4 AE rates per trial
- **Fruquintinib** — FRESCO (61.2%) / FRESCO-2 (62.7%)
- **T/T** — RECOURSE (69.4%) / SUNLIGHT (69.5%)
- **T/T + bev** — SUNLIGHT (72.4%)
- **Regorafenib** — CORRECT (78.0%)

Patient-level EQ-5D-5L questionnaire data from FRESCO-2

Preference weight sets from **Australia, Belgium, Canada, Denmark, Germany, Italy, Japan, Portugal, Singapore, South Korea, Spain, UK, and the USA** used to calculate health state-specific utility values

Univariate/multivariate mixed-effects, repeated-measures, linear regression models for each patient
- **Fixed predictors:**
  - Randomized treatment, baseline age, sex, baseline utility, and prior treatment
- **Time-variant health state covariates:**
  - Disease progression status and ongoing grade ≥3 AEs

AE-associated utility decrements = Grade ≥3 AE rates per trial × Coefficient for ongoing grade ≥3 AEs

Key take aways: Fruquintinib was associated with lower AE-associated QoL decrement versus T/T, T/T + bev, or regorafenib among patients in 13 countries across Europe, North America, and Asia with mCRC previously treated with standard therapies and biologics

Figure 1. Results from the multivariate model of FRESCO-2 data using Spanish utilities

Variable	Estimate	P-value
Intercept*	0.7785	<0.0001
Centered baseline utility†	0.6398	<0.0001
Progressive disease	−0.0448	<0.0001
Ongoing grade ≥3 AE during EQ-5D-5L visit	−0.1041	<0.0001

Indicates worsened QoL

*The mean utility in patients who were both progression-free and free of grade ≥3 AEs.
†Centered on the mean baseline utility across all patients by deducting the mean baseline utility from the baseline utility of each patient, such that the utility for a patient with the mean baseline utility = 0.

Background & Objective

- Up to 70% of patients with colorectal cancer (CRC) will experience metastatic disease (mCRC), whether at diagnosis or over the course of treatment[1,2]
- Until recently, trifluridine/tipiracil (T/T), T/T plus bevacizumab (T/T + bev), and regorafenib were the only available treatment options for patients who had previously received chemotherapy, anti-vascular endothelial growth factor (VEGF) therapy, and/or anti-epidermal growth factor receptor (EGFR) therapy (if *RAS* wild type)[3–5]
- Fruquintinib is a highly selective oral inhibitor of all three VEGF receptors (1, 2, and 3) that was approved by the US Food and Drug Administration in November 2023,[6] in the EU in June 2024,[7] in Switzerland in August 2024,[8] and in the UK,[9] Japan,[10] and Canada[11] in September 2024 for previously treated mCRC, regardless of biomarker status
- These systemic therapies all have distinct safety and tolerability profiles. Adverse events (AEs) may occur and compromise the course of treatment, increase healthcare utilization and costs, and worsen patients' quality of life (QoL)
- Treatment with regorafenib is associated with a high incidence of hand-foot syndrome,[4,12] while treatment with T/T is associated with myelosuppression,[5,13,14] and treatment with fruquintinib is associated with hypertension[6,15–17] (**Table 1**)
- A recent study compared the management costs of grade ≥3 AEs associated with fruquintinib, T/T, T/T + bev, and regorafenib for the treatment of mCRC previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy (standard therapies hereafter) and biologics in the US; the study found that fruquintinib was associated with the lowest grade ≥3 AE management costs[17]
- In mCRC, maintaining QoL is an important treatment goal alongside increasing survival, but the impact of AEs associated with systemic therapies for mCRC has not been characterized
- The objective of this analysis was to estimate the QoL impact of grade ≥3 AEs associated with fruquintinib, T/T, T/T + bev, and regorafenib among patients with previously treated mCRC based on country-specific preferences in 13 countries in Europe, North America, and Asia

Table 1. Most common grade ≥3 AEs with study treatment reported in each trial included in the analysis*

	FRESCO[15] Fruquintinib (N=278)	FRESCO-2[16] Fruquintinib (N=456)	RECOURSE[13] T/T (N=533)	SUNLIGHT[14] T/T (N=246)	SUNLIGHT[14] T/T + bev (N=246)	CORRECT[12] Regorafenib (N=500)
Rate of grade ≥3 AEs in patients who received study treatment	61.2	62.7	69.4	69.5	72.4	78.0
Most common grade ≥3 AEs with study treatment (rate)	Hypertension (21.2)	Hypertension (13.6)	Neutropenia† (37.9)	Neutropenia (32.1)	Neutropenia (43.1)	Hand-foot syndrome (16.6)
	Hand-foot syndrome (10.8)	Asthenia (7.7)	Leukopenia† (21.4)	Anemia (11.0)	Neutrophil count decreased (8.9)	Fatigue (15.4)
	Proteinuria (3.2)	Hand-foot syndrome (6.4)	Anemia† (18.2)	Neutrophil count decreased (5.3)	Anemia (6.1)	Diarrhea (8.4)

*Cross-trial comparisons should be interpreted with caution; data are for illustrative purposes only.
†The denominator is the number of patients who had at least one postbaseline measurement during treatment; n=528.

Methods

- Patient-level data from the phase 3 randomized controlled trial FRESCO-2,[16] comparing fruquintinib plus best supportive care (+ BSC) versus placebo + BSC were analyzed to estimate utility values based on responses to the EuroQoL-5-Dimension-5-Level (EQ-5D-5L) questionnaire
  - In FRESCO-2, EQ-5D-5L health questionnaires were conducted with all patients according to the following schedule: at screening; day 1 of each 28-day treatment cycle (up to cycle 20); and at the end of treatment (7 ± 3 days after last dose of therapy)
- Country-specific utility value sets were applied to the intention-to-treat population for Australia,[18] Belgium,[19] Canada,[20] Denmark,[21] Germany,[22] Italy,[23,24] Japan,[25] Portugal,[26] Singapore,[24,27] South Korea,[28] Spain,[29] UK,[30,31] and USA[32]
  - The EQ-5D-5L values were mapped to the EQ-5D-3L for Italy, Singapore, and the UK
- Univariate and multivariate mixed-effects, repeated-measures, linear regression models were conducted with random intercept for each patient to predict utility. Fixed predictors included randomized treatment (fruquintinib + BSC versus placebo + BSC), baseline age, sex, baseline utility, and prior treatment (T/T, regorafenib). Time-variant health state covariates included disease progression status and ongoing grade ≥3 AEs
- To estimate the impact of grade ≥3 AEs by treatment, the coefficient for ongoing grade ≥3 AEs was multiplied by the rates reported in pivotal phase 3 trials for each treatment to estimate their AE-associated utility decrement
- Grade ≥3 AE rates were: FRESCO[15] and FRESCO-2[16] for fruquintinib (61.2% and 62.7%), RECOURSE[13] and SUNLIGHT[14] for T/T (69.4% and 69.5%), SUNLIGHT[14] for T/T + bev (72.4%), and CORRECT[12] for regorafenib (78.0%) (**Table 1**)
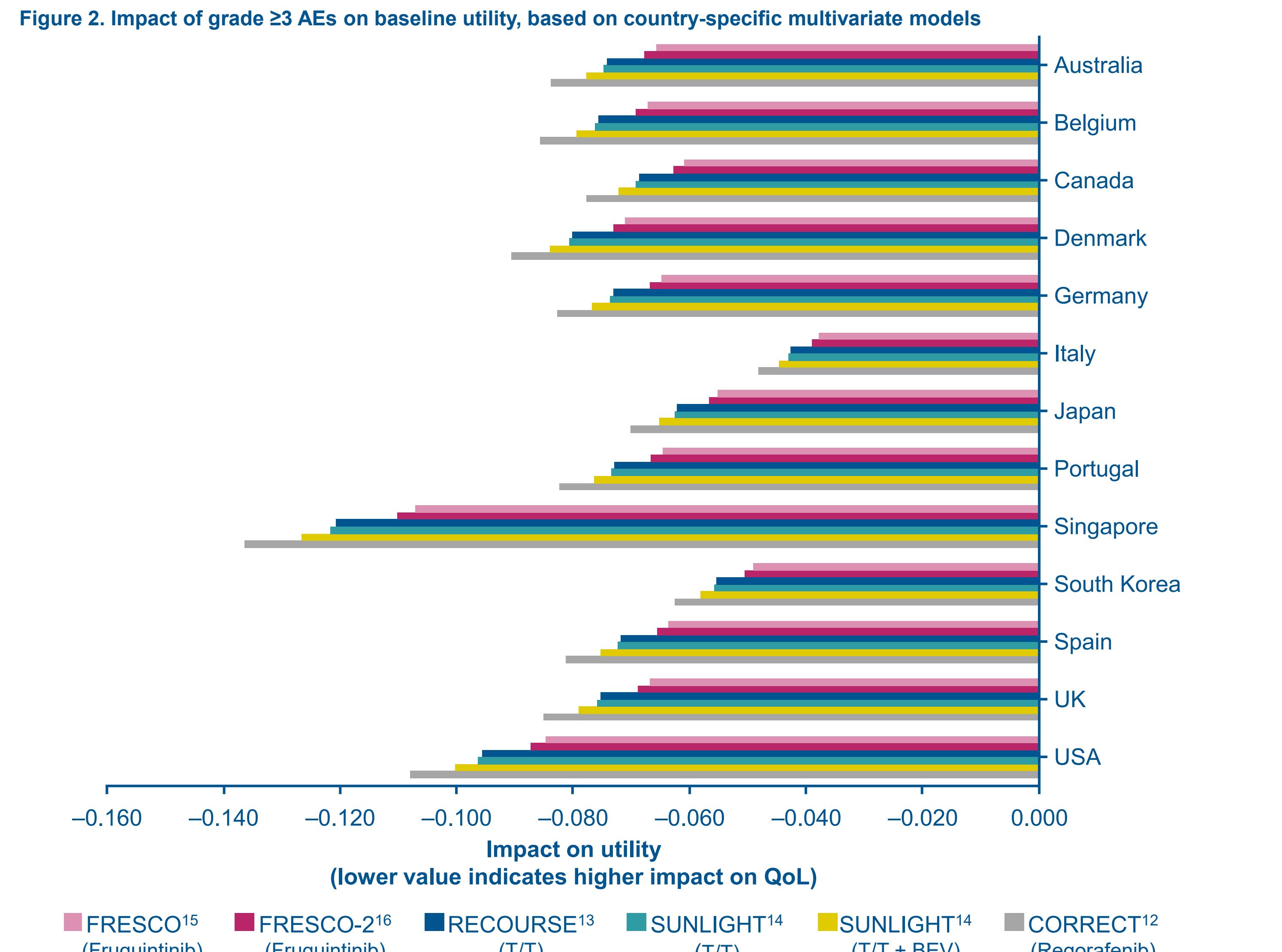
Results

- In the univariate analyses of utility scores based on FRESCO-2, none of the fixed predictors reached statistical significance across countries, including randomized treatment. Progression status and the presence of ongoing grade ≥3 AEs at the time of completion of the EQ-5D-5L questionnaire were both statistically significant and were selected for inclusion in the multivariate models
- Disease progression and ongoing grade ≥3 AEs were associated with statistically significant (P<0.0001) decreases in utility across all multivariate analyses (**Table 2**)
- **Figure 1** in the **Summary Panel** shows outcomes using Spain for illustration:
  - The mean utility for patients who were both progression-free and free of grade ≥3 AEs was 0.7785
  - The mean utility for patients with disease progression was 0.0448 lower than those without progression (P<0.0001)
  - The mean utility for patients with ongoing grade ≥3 AEs was 0.1041 lower than those without AEs (P<0.0001)
- The impact of ongoing grade ≥3 AEs on utility for each country was multiplied by the grade ≥3 AE rate of each comparator to estimate their AE-associated utility decrement (**Figure 2**)

Table 2. Results of country-specific multivariate models of utility from FRESCO-2

	Intercept*	Centered baseline utility†	Progressive disease	Ongoing grade ≥3 AE during EQ-5D visit
Australia	0.8476	0.6213	−0.0397	−0.1074
Belgium	0.7737	0.5864	−0.0474	−0.1097
Canada	0.7911	0.6253	−0.0395	−0.0996
Denmark	0.8032	0.5784	−0.0521	−0.1161
Germany	0.8259	0.5710	−0.0444	−0.1059
Italy	0.8437	0.6304	−0.0282	−0.0617
Japan	0.7652	0.6358	−0.0441	−0.0900
Portugal	0.8236	0.6349	−0.0462	−0.1056
Singapore	0.5943	0.6184	−0.0800	−0.1750
South Korea	0.7843	0.5674	−0.0347	−0.0802
Spain	0.7785	0.6398	−0.0448	−0.1041
UK	0.7191	0.6259	−0.0518	−0.1091
USA	0.7512	0.6546	−0.0588	−0.1385

*The mean utility in patients who were both progression-free and free of grade ≥3 AEs.
†Centered on the mean baseline utility across all patients by deducting the mean baseline utility from the baseline utility of each patient, such that the utility for a patient with the mean baseline utility = 0.

Figure 2. Impact of grade ≥3 AEs on baseline utility, based on country-specific multivariate models

Impact on utility (lower value indicates higher impact on QoL)

FRESCO[15] (Fruquintinib) · FRESCO-2[16] (Fruquintinib) · RECOURSE[13] (T/T) · SUNLIGHT[14] (T/T) · SUNLIGHT[14] (T/T + BEV) · CORRECT[12] (Regorafenib)

Limitations

- Given limitations around observed event rates and the frequency of data collection for the EQ-5D-5L, these analyses did not attempt to estimate or differentiate AE-specific impacts on utility and instead compared overall rates of grade ≥3 AEs across treatments
- The impact of progression and toxicity on utility was estimated based on data from FRESCO-2 only, as patient-level data were not available for other treatments
- The AE burden of treatments was estimated based on the AE rates reported in randomized controlled trials. Cross-trial comparisons may be potentially confounded by different trial designs and the nuances of the various study populations. Furthermore, patient characteristics and AEs reported in clinical trials may differ from real-world clinical practice, which may limit the generalizability of this analysis
- The coefficient for impact on utility was calculated based on grade ≥3 AEs that occurred in FRESCO-2
  - However, the most frequently occurring grade ≥3 AEs were different with each treatment, and may differ according to the number and type of prior therapies patients had received in each of the studies
  - The impact of grade ≥3 AEs on health utilities might not have been the same in CORRECT, RECOURSE, and SUNLIGHT as in the fruquintinib studies

Conclusions

- The impact of AEs associated with systemic therapies for mCRC is significant; the utility decrement associated with ongoing grade ≥3 AEs was more than double that of disease progression
- The grade ≥3 AE profile with fruquintinib is favorable; fruquintinib was associated with a lower QoL decrement versus T/T, T/T + bev, and regorafenib for patients with mCRC previously treated with standard therapies and biologics based on all country-specific value sets analyzed

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Disclosures

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