The Impact in Quality of Life of Adverse Events With Systemic Therapies for Metastatic Colorectal Cancer Previously Treated with Standard Therapies and Biologics in the United States

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Background & Objective

- Colorectal cancer (CRC) often presents at an advanced stage, with approximately 23% of patients having developed metastatic disease (mCRC) by the time of diagnosis,[1] while up to 50% of patients with localized CRC at diagnosis eventually develop metastases[2]
- Until recently, regorafenib, trifluridine/tipiracil (T/T) and T/T + bevacizumab (T/T + bev) were the only available treatment options for patients who had previously received chemotherapy, anti-VEGF therapy, and/or anti-EGFR therapy (if *RAS* wild type)[3-5]
- Fruquintinib is a highly selective, oral inhibitor of all three VEGF receptors (VEGFRs -1, -2, and -3) that was approved by the US FDA in November 2023 for previously treated mCRC, regardless of biomarker status[6]
- 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,[4,7] while treatment with T/T is associated with myelosuppression[5,8-9] (**Table 1**)
  - Treatment with fruquintinib is associated with hypertension[6,10-11] (**Table 1**)

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

FRESCO Fruquintinib (*N*=278)[10]	FRESCO-2 Fruquintinib (*N*=456)[11]	CORRECT Regorafenib (*N*=500)[7]	RECOURSE T/T (*N*=528)[8]	SUNLIGHT T/T (*N*=246)[9]	SUNLIGHT T/T+bev (*N*=246)[9]
Hypertension (21.2%)	**Hypertension** (13.6%)	**Hand-foot syndrome** (16.6%)	**Neutropenia** (37.9%)	**Neutropenia** (32.1%)	**Neutropenia** (43.1%)
Hand-foot syndrome (10.8%)	**Asthenia** (7.7%)	**Fatigue** (15.4%)	**Leukopenia** (21.4%)	**Anemia** (11.0%)	**Neutrophil count decreased** (8.9%)
Proteinuria (3.2%)	**Hand-foot syndrome** (6.4%)	**Diarrhea** (8.4%)	**Anemia** (18.2%)	**Neutrophil count decreased** (5.3%)	**Anemia** (6.1%)

*Cross-trial comparisons should be interpreted with caution; data are for illustrative purposes only.

- A recent study compared the management costs of grade ≥3 AEs associated with fruquintinib, regorafenib, T/T, and T/T + bev 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[12]
- 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, regorafenib, T/T, and T/T + bev for patients with previously treated mCRC from the US patient perspective

Methods

- Patient-level data from the phase 3 randomized clinical trial FRESCO-2, comparing fruquintinib + best supportive care (BSC) vs placebo + BSC were analyzed to estimate utility values based on responses to the EuroQoL-5-Dimension-5-Level (EQ-5D-5L) questionnaire
  - The EQ-5D-5L is a widely validated and used generic instrument that measures a patient's self-reported health status based on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The patient is asked to indicate their health state by ticking the box next to the most appropriate statement in each of the five dimensions. This decision results in a 1-digit number that expresses the level selected for that dimension (1=no problems, 5=extreme problems). The digits for the five dimensions can be combined into a 5-digit number that describes the patient's health state[13] (**Figure 2**)
  - Each health state can potentially be assigned a summary index score based on societal preference weights for the health state. These weights, often referred to as 'utilities', represent a preference-based measure of health-related QoL for each health state, measured on a 0 (health state equivalent to death) to 1 (perfect health) scale represent a preference-based measure of health-related QoL for each health state, measured on a 0 (health state equivalent to death) to 1 (perfect health) scale
  - The health state preferences can differ between countries/regions, so country specific value sets are used to convert each possible health state (e.g., 21325 or 21111 in **Figure 2**) to a utility value. In this analysis, the US-specific value set was used to calculate health state-specific utility values[14]
    - The US-specific value set was previously derived via an international, standardized protocol developed by the EuroQol Group, using data from 1,134 US respondents who completed the EQ-5D-5L questionnaire[14]
- In FRESCO-2, EQ-5D-5L health questionnaires were administered for 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 (30±3 days after last dose of therapy)
- Univariate and multivariate mixed-effects, repeated-measures, linear regression models were fitted with random intercept to account for longitudinal data. Fixed predictors included randomized treatment (fruquintinib + BSC vs placebo + BSC), baseline age, sex, baseline utility, and prior treatment (regorafenib, T/T). 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 (any unresolved grade ≥3 treatment-emergent AEs at the time of the utility measurement) was multiplied by the rates from each treatment's pivotal Phase 3 trial to estimate their AE-associated utility decrement
- Grade ≥3 AEs rates were: FRESCO and FRESCO-2 for fruquintinib (61.2% and 63.0%),[10,11] CORRECT for regorafenib (78.0%),[7] RECOURSE and SUNLIGHT for T/T (69.0% and 69.5%),[8,9] and SUNLIGHT for T/T + bev (72.4%)[9]

Question How do grade ≥3 AEs impact the QoL of US patients with previously treated mCRC receiving either fruquintinib, regorafenib, T/T, or T/T + bev?

Methods

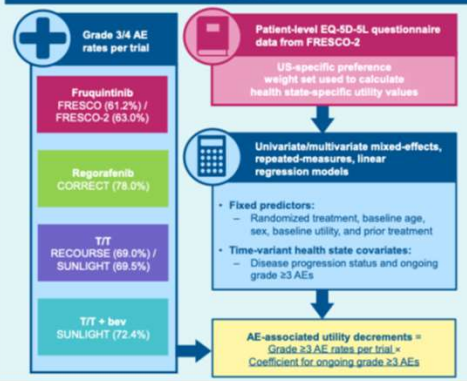
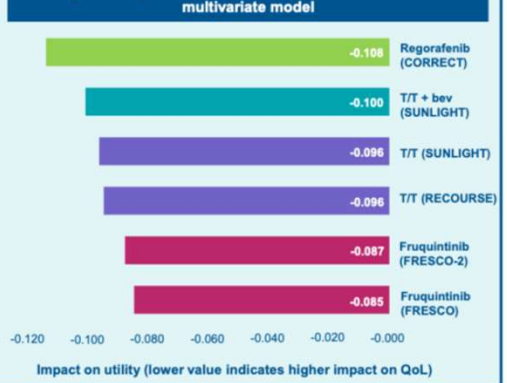
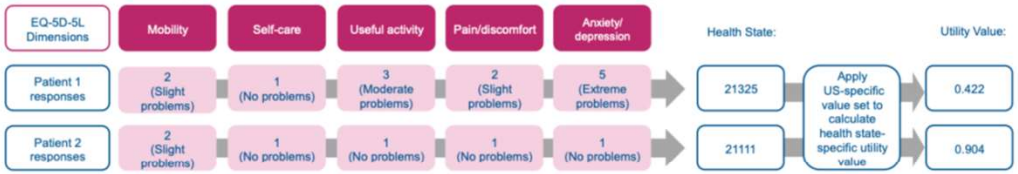


Figure 1. Impact on utility from grade ≥3 AEs based on multivariate model



Key take aways Fruquintinib was associated with lower AE-associated QoL decrement vs regorafenib, T/T, and T/T + bev for US patients with mCRC previously treated with standard therapies and biologics

Figure 2. Illustrative example of EQ-5D-5L questionnaire responses, health states, and utility value estimation



Results

- In the univariate analyses of utility scores based on FRESCO-2, none of the fixed predictors reached statistical significance (**Table 2**). Progression status and the presence of ongoing grade ≥3 AEs at the time the EQ-5D-5L was collected were both statistically significant and were selected for inclusion in the multivariate model
- Disease progression and ongoing grade ≥3 AEs were associated with statistically significant decreases in utility in the multivariate analyses (**Table 3**)
  - On a scale of 0 (health state equivalent to death) to 1 (perfect health), the mean utility for patients who were both progression-free and free of grade ≥3 AEs was 0.7512
  - The mean utility of patients with disease progression was 0.0588 lower than those without progression (p <0.0001)
  - The mean utility of patients with ongoing grade ≥3 AEs was 0.1385 lower than those without grade ≥3 AEs (p <0.0001)
- For each of the trials analyzed, the calculated AE-associated utility decrements were greater than the minimally important difference threshold for EQ-5D-5L scores for US patients with cancer, estimated to be 0.06[15] (**Summary Panel, Figure 1**)

Table 2. Results of univariate models of utility from FRESCO-2 for all potential predictors

Univariate predictor	Estimate	Standard error	P-value
Fruquintinib + BSC (vs placebo + BSC)	0.0245	0.0174	0.1602
Centered baseline age*	-0.0013	0.0008	0.1151
Female (vs male)	0.0121	0.0158	0.4462
Prior regorafenib (vs no prior regorafenib)	0.0600	0.0293	0.0411
Prior T/T (vs no prior T/T)	0.0257	0.0166	0.1225
Progressive disease (vs not progressed)†	-0.0666	0.0112	<0.0001
Ongoing grade ≥3 AE during EQ-5D-5L visit†	-0.1545	0.0182	<0.0001

Indicates worsened QoL. Indicates improved QoL.

*Centered on the mean baseline age across all patients by deducting the mean baseline age from the baseline age for each patient, such that the age for a patient with the mean age = 0. †Time dependent covariate.

Table 3. Results of multivariate model of utility from FRESCO-2

Variable	Estimate	P-value
Intercept*	**0.7512**	<0.0001
Centered baseline utility†	**0.6546**	<0.0001
Progressive disease	-0.0588	<0.0001
Ongoing grade ≥3 AE during EQ-5D visit	-0.1385	<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.

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 clinical 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, as the most frequently occurring grade ≥3 AEs were different with each treatment, the impact that they had 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 vs regorafenib, T/T, and T/T + bev for US patients with mCRC previously treated with standard therapies and biologics

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