Quality-adjusted Time Without Symptoms of disease or Toxicity (Q-TWiST) analysis of fruquintinib + best supportive care (BSC) compared with placebo + BSC in metastatic colorectal cancer (mCRC): Results from the FRESCO-2 trial

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Background

- Fruquintinib, a highly selective, oral inhibitor of all three VEGF receptors (VEGFRs -1, -2, and -3),[1] was approved in China in 2018 as third or later line of therapy for mCRC, based on the results from the phase 3 FRESCO study (NCT02314819)[2]
- The global, phase 3 FRESCO-2 study (NCT04322539) investigated the efficacy and safety of fruquintinib + BSC in a population that better reflected patient characteristics and current treatment practices outside of China[3]
  - Patients enrolled in FRESCO-2 had received all standard cytotoxic and targeted therapies and had progressed on, or were intolerant to, TAS-102 or regorafenib, or both
  - Fruquintinib + BSC resulted in a median overall survival (OS) improvement of 2.6 months compared with placebo + BSC (7.4 vs 4.8 months; hazard ratio [HR] 0.66; 95% confidence interval [CI], 0.55–0.80; p<0.001)
  - Fruquintinib + BSC was well tolerated without deterioration of quality of life (QoL),[4] with a safety profile consistent with the previously established monotherapy profile, and no new safety concerns were identified
- Based on the results from FRESCO and FRESCO-2, fruquintinib was approved by the US FDA for previously treated mCRC, regardless of biomarker status[3,5]
- As mCRC and its treatment can adversely impact QoL, maintaining QoL is an important treatment goal in addition to improving survival outcomes, particularly as patients progress through lines of therapy
- Q-TWiST measures the quality of patients' survival by assessing the proportion of survival time that is free of symptoms or toxicity; it can be used to inform clinical decision making by integrating patient preferences with clinical data. It is a quality-adjusted life-year metric that can be used in oncology treatment assessment as a proxy for the patient QoL that is typically assessed through patient-reported outcomes[6]
  - Q-TWiST analysis of the FRESCO study demonstrated that fruquintinib + BSC provided a clinically meaningful quality-adjusted survival benefit versus placebo + BSC in Chinese patients[7]

Objective

- To compare the benefit-risk of fruquintinib + BSC with that of placebo + BSC among all patients who were randomized in FRESCO-2, using Q-TWiST methodology

Methods

- This was a *post-hoc* Q-TWiST analysis based on individual-level patient data from all patients in the FRESCO-2 study who were randomized to receive fruquintinib + BSC (*n*=461) or placebo + BSC (*n*=230)
- The survival time (months) for each patient was partitioned into three health states
  - **TOX:** Time spent with grade 3 or 4 treatment-emergent adverse events (TEAEs) after randomization and before disease progression (any day with multiple grade 3 or 4 TEAEs was only counted once)
  - **TWiST:** Time from randomization to disease progression without TOX
  - **REL:** Time from disease progression to death or censoring
- Assuming a utility coefficient of 1 to account for 100% of the duration of TWiST (U_{TWiST}), and of 0.5 to account for 50% of the duration of TOX (U_{TOX}) and REL (U_{REL}), Q-TWiST was calculated as the utility-weighted sum of the mean durations of each health state
  - Q-TWiST = (TOX × U_{TOX}) + (TWiST × U_{TWiST}) + (REL × U_{REL})
- The mean time spent in each of the health states was calculated for each treatment group using Kaplan–Meier estimation, and 95% CIs for the differences between treatment groups were calculated using the z-method, while bootstrapping was used to calculate standard errors
- The relative improvement (%) of Q-TWiST for the fruquintinib + BSC group was calculated by dividing the Q-TWiST difference by the mean OS in the placebo + BSC group
  - Relative Q-TWiST improvements of >10% imply a 'clinically important' difference; improvements of >15% suggest a 'clearly clinically important' difference[8]
- Selected *post-hoc* subgroup analyses were conducted, stratified by the characteristics that were most relevant to disease progression and OS: age (<65 years; ≥65 years); sex (male; female); liver metastases at baseline (yes; no); number of prior lines for metastatic disease (≤3; >3), and by primary site of tumor at first diagnosis (colon left; colon right; colon unknown; rectum only; colon left and right)
- Considering that serious AEs can impact patients' QoL and their ability to tolerate active treatments, a sensitivity analysis was conducted to ensure that the conclusion from the primary Q-TWiST analysis was robust in terms of toxicity:
  - Q-TWiST was re-derived using any serious TEAE instead of grade 3 or 4 TEAEs in the TOX state, and the analysis was repeated

Question Does fruquintinib + BSC demonstrate a quality-adjusted survival benefit versus placebo + BSC in patients enrolled in FRESCO-2?

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

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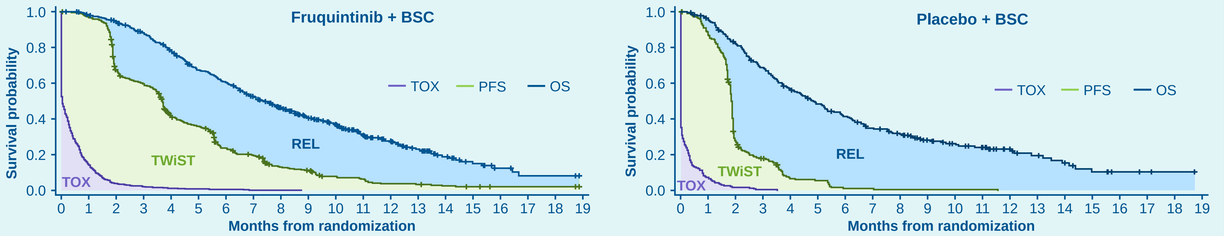
- **Fruquintinib (*n*=461)** 5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)
- **Placebo (*n*=230)** 5 mg PO, QD + BSC, 28-day cycle (3 weeks on, 1 week off)

Treatment until progressive disease or unacceptable toxicity

Primary endpoint: OS
Key secondary endpoint: PFS
Other secondary endpoints: ORR, DCR, DoR, Safety, HRQoL
***Post-hoc* analysis:** Q-TWiST

Figure 1: Kaplan–Meier curves for OS (blue), PFS (green), and toxicity (purple)



TOX: Time spent with grade 3 or 4 TEAEs after randomization and before disease progression (any day with multiple grade 3 or 4 TEAEs was only counted once)

TWiST: Time from randomization to disease progression without TOX

REL: Time from disease progression to death or censoring

Q-TWiST = (TOX × U_{TOX}) + (TWiST × U_{TWiST}) + (REL × U_{REL})

	Fruquintinib + BSC	Placebo + BSC
Q-TWiST, months (95% CI)	6.25 (5.89–6.61)	4.21 (3.81–4.60)
Difference (95% CI), p-value	2.04 (1.51–2.57), p<0.05	

Key conclusions Fruquintinib + BSC demonstrated a clinically meaningful quality-adjusted survival benefit compared with placebo + BSC in heavily pretreated patients with refractory mCRC enrolled in FRESCO-2

DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life; ORR, objective response rate; PFS, progression-free survival

Results

- Kaplan–Meier curves for OS, PFS, and toxicity are shown for fruquintinib + BSC and placebo + BSC (**Summary Panel Figure 1**); the area between the curves illustrates the time that patients spent in each of the three health states for the Q-TWiST calculation
- The mean duration of each health state by treatment group for the primary analysis is summarized in **Table 1**
  - Fruquintinib + BSC demonstrated a significantly longer mean duration of Q-TWiST, TWiST, and TOX, and a shorter mean duration of REL versus placebo + BSC
  - Q-TWiST was significantly improved with fruquintinib + BSC versus placebo + BSC, with a Q-TWiST difference of 2.04 months (6.25 versus 4.21 months) and relative improvement of 31.4% in favor of fruquintinib + BSC
  - This effect was mainly driven by the difference in the TWiST component

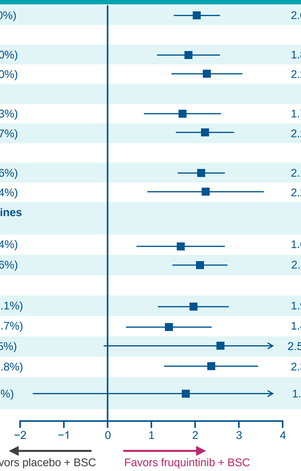
Table 1. Mean duration of health states

Health state	Mean duration, months (95% CI)	
	Fruquintinib + BSC (*n*=461)	Placebo + BSC (*n*=230)
Q-TWiST	6.25 (5.89–6.61)	4.21 (3.81–4.60)
Difference (95% CI), p-value	2.04 (1.51–2.57), p<0.05	
TWiST	4.06 (3.75–4.36)	1.92 (1.75–2.10)
Difference (95% CI), p-value	2.14 (1.78–2.49), p<0.05	
TOX	0.45 (0.37–0.53)	0.21 (0.15–0.28)
Difference (95% CI), p-value	0.24 (0.13–0.34), p<0.05	
REL	3.93 (3.55–4.32)	4.36 (3.75–4.96)
Difference (95% CI), p-value	-0.43 (-1.15–0.29), p≥0.05	

- Subgroup analyses suggested consistent Q-TWiST improvements in all subgroups, except in patients whose primary tumor site was unknown or in those with both left- and right-sided tumors (this is due to very small number of patients in these subgroups) (**Figure 2**)
- The results from the sensitivity analysis demonstrated the robustness of the primary analysis: Q-TWiST was 6.41 months for fruquintinib + BSC versus 4.26 months for placebo + BSC, leading to a mean Q-TWiST difference of 2.14 months (95% CI 1.61–2.68; p<0.05) and a relative improvement of 33.0%

Figure 2. Differences in Q-TWiST by subgroup

Subgroup	Patients, *n* (%)	Mean difference (95% CI)	Improvement (%)
Overall	691 (100%)	2.04 (1.51–2.57)	31.43
Age			
<65	366 (53.0%)	1.85 (1.13–2.57)	28.51
≥65	325 (47.0%)	2.27 (1.46–3.08)	34.98
Sex			
Female	306 (44.3%)	1.71 (0.83–2.59)	26.35
Male	385 (55.7%)	2.23 (1.56–2.89)	34.36
Liver metastases			
Yes	495 (71.6%)	2.14 (1.60–2.68)	32.97
No	196 (28.4%)	2.24 (0.91–3.57)	34.51
Number of prior treatment lines for metastatic disease			
≤3	189 (27.4%)	1.67 (0.66–2.68)	25.73
>3	502 (72.6%)	2.11 (1.48–2.74)	32.51
Primary site			
Colon left	284 (41.1%)	1.96 (1.15–2.77)	30.20
Colon right	150 (21.7%)	1.40 (0.42–2.38)	21.57
Colon unknown	38 (5.5%)	2.58 (−0.09–5.26)	39.75
Rectum only	213 (30.8%)	2.37 (1.29–3.44)	36.52
Colon left and right	6 (0.9%)	1.79 (-1.7–5.29)	27.58



Conclusions

- The Q-TWiST analysis can evaluate trade-offs between potential treatment toxicities and survival time, which is clinically important for treatment decision making in later line mCRC for patients whose QoL has been worsened by their disease and the prior therapies received
- Fruquintinib + BSC demonstrated a significant and clinically meaningful improvement in Q-TWiST versus placebo + BSC in FRESCO-2 patients
  - There was a Q-TWiST improvement of 2.04 months with fruquintinib + BSC versus placebo + BSC (6.25 versus 4.21 months; 95% CI 1.51–2.57; p<0.05)
  - The improvement is mostly consistent across key subgroups and is robust, supported by the sensitivity analysis
- *Post-hoc* Q-TWiST showed that fruquintinib delays disease progression and prolongs patient survival without substantially increasing toxicity, which is particularly notable when considering the toxicity was evaluated against an inactive comparator (i.e., placebo)
- Fruquintinib has the potential to provide an improved survival benefit with QoL for patients with previously treated mCRC who have limited treatment options

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