European Journal of Cancer 218 (2025) 115268

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

Health-related quality of life associated with fruquintinib in patients with metastatic colorectal cancer: Results from the FRESCO-2 study

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ARTICLE INFO

Keywords:
Metastatic colorectal cancer
Health-related quality of life
EORTC QLQ-C30
EQ-5D-5L
Fruquintinib

ABSTRACT

Introduction: Maintaining or improving health-related quality of life (HRQoL) is as important as extending survival in metastatic colorectal cancer. We report an HRQoL analysis from FRESCO-2 (NCT04322539).
Methods: Patients were randomized to fruquintinib +best supportive care (BSC; n = 461) or placebo +BSC (n = 230). Instruments of EORTC QLQ-C30 and 5-level EQ-5D, and ECOG performance status (PS) were assessed. Changes from baseline scores for QLQ-C30 and EQ-5D were evaluated and minimally important difference thresholds were used to define stable, improved, or deteriorated QoL. Time to deterioration (TTD) was assessed.
Results: With fruquintinib versus placebo, baseline QLQ-C30 global health status (GHS) and EQ-5D visual analog scale (VAS) scores were 65.2 versus 64.6 and 67.0 versus 66.6, respectively. Least-squares mean changes from baseline fluctuated throughout treatment. At end of treatment (EOT), mean scores with fruquintinib versus placebo were 53.8 versus 52.3 (QLQ-C30 GHS) and 58.9 versus 58.5 (EQ-5D VAS). For QLQ-C30 GHS, 38.3 % versus 36.5 % of patients receiving fruquintinib versus placebo had stable or improved scores at EOT; median TTD was 2.1 versus 1.8 months (HR, 0.9; 95 % CI, 0.7–1.0). For EQ-5D VAS, 47.9 % versus 42.7 % had stable or improved scores at EOT; median TTD was 2.6 versus 1.9 months (HR, 0.8; 95 % CI, 0.6–0.9). Median TTD to ECOG PS ≥ 2 or death within 30+ /7 days after EOT was 6.6 versus 2.9 months with fruquintinib versus placebo (HR, 0.6; 95 % CI, 0.4–0.7).
Conclusions: Fruquintinib delayed TTD of ECOG PS and did not negatively impact HRQoL versus placebo.

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https://doi.org/10.1016/j.ejca.2025.115268
Received 25 October 2024; Received in revised form 24 January 2025; Accepted 28 January 2025
Available online 29 January 2025

1. Introduction

The management of metastatic colorectal cancer (mCRC) primarily focuses on prolongation of patient survival [1,2]. However, maintaining or improving health-related quality of life (HRQoL) is an important goal in addition to increasing duration of life [2–4]. HRQoL is impacted by disease burden, such as a recent diagnosis, physical symptoms, comorbidities, disease progression/recurrence, or adverse events (AEs) as a consequence of disease or treatment [1–3,5]. As such, the burden of mCRC affects psychological and emotional wellbeing, social/family interactions, physical functioning, and the ability to carry out daily activities, which may severely impact patients' HRQoL.

HRQoL is commonly a patient-reported outcome (PRO) assessed using instruments such as the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30). Moreover, using measures that are assessed by physicians can complement PROs and inform treatment decisions [6,7]. Eastern Cooperative Oncology Group performance status (ECOG PS) is a physician-assessed indicator of a patient's level of physical functioning that is widely used in oncology clinical studies [6]. Importantly, ECOG PS and patient-reported HRQoL at baseline have been shown to be independent prognostic indicators for overall survival (OS) in patients with mCRC [7]. Therefore, maintaining stable or improved HRQoL and ECOG PS in this patient population is critical to survival, and both measures are recognized as endpoints to evaluate the efficacy of treatments in clinical studies [6,8–10].

Fruquintinib is a highly selective oral inhibitor of all three vascular endothelial growth factor receptors (VEGFRs −1, −2, and −3) [11] that was approved in China in September 2018 as third or later line of therapy for mCRC based on the results of the phase 3 FRESCO study (NCT02314819) [12,13]. FRESCO met its primary endpoint of improvement in OS with fruquintinib plus best supportive care (+BSC) versus placebo+BSC (median 9.3 vs 6.6 months; hazard ratio [HR], 0.65; $P < 0.001$) [12]. At the time of FRESCO, treatment patterns for mCRC in China differed from those in the rest of the world. The global, phase 3 FRESCO-2 study (NCT04322539) was designed to investigate fruquintinib in a population that better reflected patient characteristics and treatment practices outside of China [14]. In FRESCO-2, fruquintinib+BSC versus placebo+BSC was associated with significant improvement in OS (median 7.4 vs 4.8 months; HR, 0.66; $P < 0.001$) and was well tolerated, with a safety profile consistent with the previously established monotherapy profile [14]. Based on the results of FRESCO and FRESCO-2, fruquintinib was approved in November 2023 by the US Food and Drug Administration for the treatment of adult patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if *RAS* wild-type and medically appropriate, an anti-EGFR therapy. Based on FRESCO-2 data, fruquintinib was subsequently approved in June 2024 in the European Union for the treatment of adults patients with mCRC who have been previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil (TAS-102) or regorafenib [15,16].

Here we report for the first time the pre-planned HRQoL analysis of patients who received fruquintinib or placebo in the FRESCO-2 study.

2. Materials and methods

2.1. Patients and study design

The design of FRESCO-2 has been described previously [14]. Patients were randomized 2:1 to receive fruquintinib 5 mg or matching placebo by mouth daily on days 1–21 in 28-day cycles, +BSC. The primary endpoint was OS. Secondary endpoints included changes in HRQoL and health state assessed using EORTC QLQ-C30 and EuroQoL 5 Dimension 5 Level (EQ-5D-5L) questionnaires [14].

2.2. Assessments and endpoints

Patient-reported data from QLQ-C30 and EQ-5D questionnaires were collected digitally at baseline and on day 1 of each cycle in line with study treatment visits, until end of treatment (EOT). The denominator to calculate questionnaire completion rates at baseline and each cycle was the total number of patients who were still receiving treatment at the time of cycle assessment and were expected to complete the questionnaires, irrespective of actual visit attendance. The QLQ-C30 questionnaire, composed of both multi-item scales and single-item measures, is a 30-item cancer-specific instrument grouped into 15 subscales: overall global health status (GHS)/QoL score; five functioning scores (physical, role, emotional, cognitive, and social); three composite symptom scores (fatigue, pain, and nausea and vomiting); and six single-symptom items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) [17]. The EQ-5D questionnaire comprises a 5-component scale: mobility, self-care, usual activity, pain/discomfort, and anxiety/depression [18]; and a general visual analog scale (VAS) for health status [19,20]. Scoring of QLQ-C30 and EQ-5D questionnaires are detailed in Supplementary Appendix.

For post-baseline visits, change from baseline scores of the subscales from QLQ-C30, EQ-5D index score, and VAS were calculated. Minimally important difference (MID) thresholds for each scale and item were used to define stable, improved, and deteriorated QoL (Supplementary Table 1) [18,21–23]. Time to deterioration (TTD) using MIDs was a *post-hoc* assessment and was calculated as time (months) from randomization until first deterioration, or death, whichever came first.

The ECOG PS of patients was assessed by the investigator at baseline, on day 21 of cycle 1, days 1 and 21 of cycles 2 and 3, on day 1 only from cycle 4 onwards, at EOT, and at safety follow up, which was 30+/−7 days after EOT (maximum of 37 days). ECOG PS scoring is detailed in Supplementary Appendix. All enrolled patients had a baseline ECOG PS score of 0 or 1. TTD of ECOG PS was a *post-hoc* assessment and was investigated via Kaplan–Meier analysis of time (months) from randomization to first occurrence of ECOG PS ≥ 2 or death, either within 30+/−7 days of the last dose received or overall.

2.3. Statistical analysis

All available data of the patients who withdrew from the FRESCO-2 study for any reason was analyzed and missing data was assumed to be missing at random. Patients with missing data were excluded from analyses for which data were not available. Categorization occurred at each visit with the evaluable patients from the intent to treat (ITT) population. When an intercurrent event of death or treatment discontinuation occurred, patients were no longer included in the QLQ-C30 and EQ-5D analyses from that timepoint onward. At each post-baseline visit, the least-squares means (LSM) and LSM difference (95 % confidence interval [CI]) between fruquintinib and placebo were calculated from a mixed model repeated measures (MMRM) model (Supplementary Appendix). The number and percentage of patients achieving QoL status (i.e. improvement, stable, and deterioration) for each QLQ-C30 and EQ-5D scale were summarized descriptively by visit and treatment group. Analyses of QLQ-C30 and EQ-5D scales were conducted in all randomized patients who had baseline and ≥ 1 post-baseline non-missing assessment. With QLQ-C30 and EQ-5D assessments, an analysis of covariance (ANCOVA) was conducted for the last assessment during treatment period as a sensitivity analysis of the impact of intercurrent events such as death and drop-out (Supplementary Appendix). The treatment period was defined as the date of randomization to 30+/−7 days after the last dose. *Post-hoc* assessments of TTD using MIDs and TTD to ECOG PS ≥ 2 were assessed in the ITT population using Kaplan–Meier method, and *P*-values were obtained from stratified log-rank test. HRs (95 % CI) were calculated from

a stratified Cox model in which treatment and baseline score were included as fixed effects.

3. Results

3.1. Patients

In FRESCO-2, baseline demographics and disease characteristics were generally balanced between fruquintinib (n = 461) and placebo (n = 230) arms. Efficacy and safety data have been reported previously [14].

3.2. Treatment duration and questionnaire completion rates

In FRESCO-2, patients received a median of 3 treatment cycles with fruquintinib (range 1–20) and 2 with placebo (range 1–13). Overall, 48.9 % of patients in the fruquintinib arm and 14.8 % in the placebo arm received ≥ 4 cycles. At baseline, in the fruquintinib and placebo arms, respectively, 91.1 % and 94.3 % of patients completed the QLQ-C30 questionnaire, and 91.3 % and 95.7 % completed the EQ-5D questionnaire. In the fruquintinib and placebo arms, questionnaire completion rates up to cycle 5 were ≥ 85.1 % and ≥ 84.1 % for QLQ-C30, and ≥ 86.3 % and ≥ 87.3 % for EQ-5D (Supplementary Table 2).

3.3. EORTC QLQ-C30 and EQ-5D-5L outcomes

Mean QLQ-C30 GHS baseline scores in the fruquintinib versus placebo arms were 65.2 (standard deviation [SD], 19.9) versus 64.6 (SD, 19.7); mean EQ-5D VAS baseline scores were 67.0 (SD, 19.0) versus 66.6 (SD, 20.3) (Supplementary Table 3). Mean scores fluctuated in both arms throughout treatment. For QLQ-C30 GHS, the LSM changes from baseline with fruquintinib versus placebo were −2.1 versus −3.7 at cycle 2, and −4.5 versus −6.1 at cycle 3; for EQ-5D VAS, LSM changes from baseline were −0.3 versus −0.9 at cycle 2, and −1.1 versus −2.5 at cycle 3 (Fig. 1). At EOT, mean QLQ-C30 GHS scores with fruquintinib versus placebo were 53.8 (SD, 21.6) versus 52.3 (SD, 24.3) and mean EQ-5D VAS scores were 58.9 (SD, 20.0) versus 58.5 (SD, 20.7) (Supplementary Table 3).

The percentages of patients whose QLQ-C30 GHS scores remained stable (MID −6.38 to <8.43) or improved (≥8.43) fluctuated throughout treatment, and at any time during fruquintinib versus placebo treatment (post-baseline), the maximum percentages of patients with stable or improved scores were 72.4 % versus 58.6 % and minimum percentages were 25.5 % versus 30.9 %. At EOT, percentages were comparable between the fruquintinib and placebo arms (38.3 % vs 36.5 %) (Fig. 2).

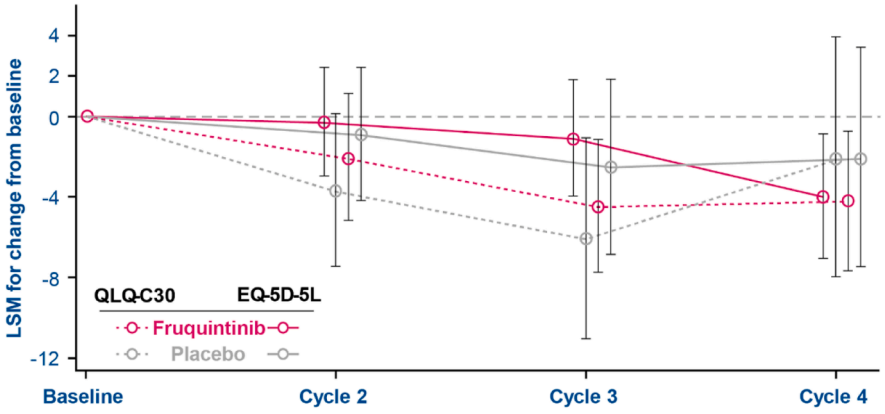
The EQ-5D VAS scores also fluctuated throughout the duration of treatment. The maximum percentages of patients who remained stable (MID −7 to <7) or improved (MID ≥7) with fruquintinib versus placebo treatment post-baseline were 75.3 % and 63.8 %, and minimum percentages were 34.8 % versus 35.1 %; percentages were 47.9 % versus 42.7 % at EOT (Fig. 3).

Based on predefined MIDs, the median TTD with fruquintinib versus placebo was 2.1 versus 1.8 months (HR, 0.9; 95 % CI, 0.7–1.0) for QLQ-C30 GHS (Fig. 4, Supplementary Fig. S1), 2.6 versus 1.9 months (HR, 0.8; 95 % CI, 0.6–0.9) for EQ-5D VAS, and 3.0 versus 1.0 (HR, 0.8; 95 % CI, 0.7–1.0) for EQ-5D index scores (Fig. 4). Among QLQ-C30 subscales, median TTD for dyspnea (HR, 0.7), insomnia (HR, 0.8), and financial difficulty (HR, 0.8) had HRs of < 1 with 95 % CIs that did not cross 1 (Fig. 4).

3.4. ECOG PS outcomes

The proportions of patients in the safety population (who received at least one dose of fruquintinib or placebo for the specific cycle) who had baseline ECOG PS scores of 0 and 1 were balanced between fruquintinib and placebo arms (ECOG PS 0: 42.3 % vs 45.6 %; ECOG PS 1: 57.7 % vs 54.4 %) (Fig. 5). The percentage of patients with an on-treatment increase of ≥ 1 point in ECOG PS from baseline was 52.1 % with fruquintinib versus 54.0 % with placebo.

TTD to ECOG PS ≥ 2 or death was improved with fruquintinib versus placebo; patients in the ITT population who received fruquintinib versus placebo had a longer median TTD to ECOG PS ≥ 2 or death within 30+ /



Patients, n	Baseline	Cycle 2	Cycle 3	Cycle 4
QLQ-C30				
Fruquintinib	420	330	229	182
Placebo	217	149	53	29
EQ-5D-5L				
Fruquintinib	421	337	232	185
Placebo	220	151	54	30

Fig. 1. LSM change (95 % CI) from baseline in QLQ-C30 GHS and EQ-5D-5L VAS scores (ITT population; fruquintinib n = 461, placebo n = 230). Includes evaluable patients at each cycle from the ITT population. A higher QLQ-C30 GHS and EQ-5D-5L VAS score indicates a better overall condition. Abbreviations: CI, confidence interval; EQ-5D-5L VAS, EuroQoL 5 Dimension 5 Level visual analog scale; ITT, intent-to-treat; LSM, least squares mean; QLQ-C30 GHS, Quality of Life Questionnaire Core 30 global health status.

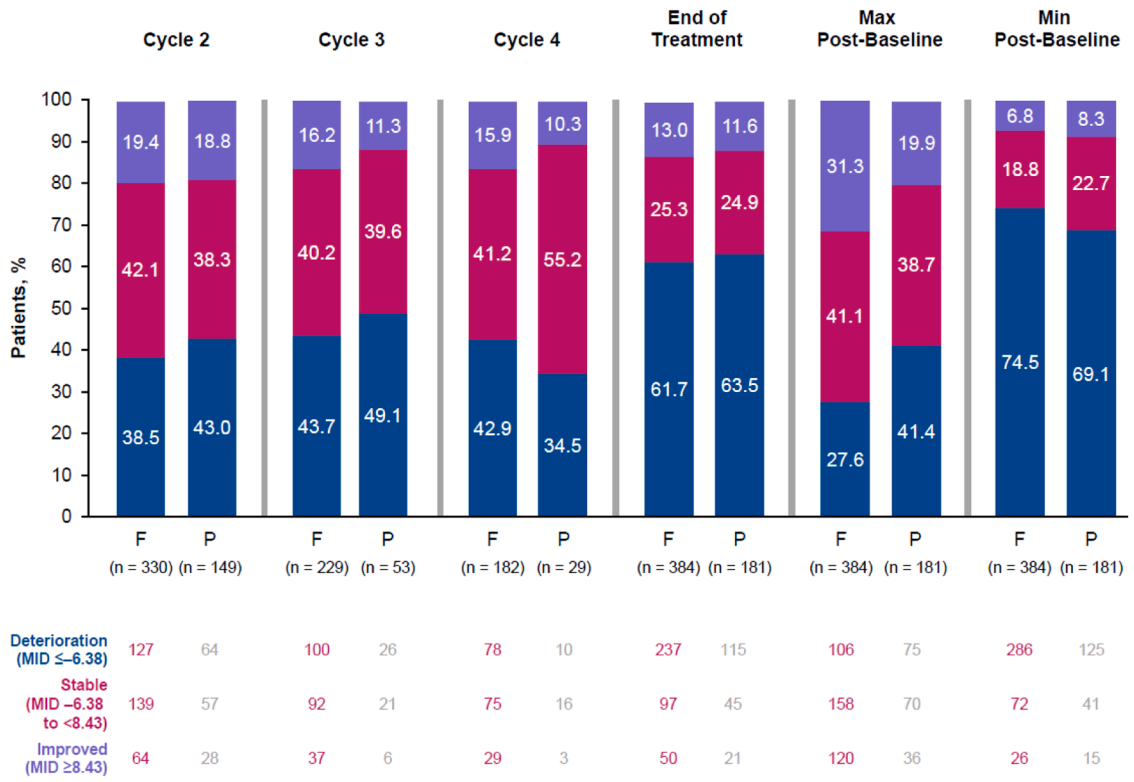


Fig. 2. Baseline and post-baseline assessment of patient health status according to QLQ-C30 GHS scores (ITT population; fruquintinib n = 461, placebo n = 230). Percentages are based on the number of patients who received at least one dose of fruquintinib or placebo for the specific cycle (evaluable patients at each cycle from the ITT population). Percentages are based on n, the number of patients with a non-missing result for the given visit. The maximum post-baseline score represents the best condition during the treatment period; the minimum post-baseline score represents the worst condition during treatment. MID thresholds were as follows: deterioration MID ≤ −6.38, stable MID −6.38 to < 8.43, and improved ≥ 8.43 [22]. Abbreviations: F, fruquintinib; ITT, intent-to-treat; MID, minimally important difference; P, placebo; QLQ-C30 GHS, Quality of Life Questionnaire Core 30 global health status.

−7 days after EOT (6.6 vs 2.9 months; HR, 0.6; 95 % CI, 0.4–0.7) (Fig. 6); when deaths within 30+ /−7 days of EOT were censored (7.9 vs 4.9 months; HR, 0.7; 95 % CI, 0.5–0.8) (Supplementary Fig. S2A); and when all deaths observed during the study were included in the analysis and not censored (5.3 vs 2.9 months; HR, 0.6; 95 % CI, 0.5–0.8) (Supplementary Fig. S2B).

4. Discussion

Patients with refractory mCRC have a high disease burden that affects their QoL [24–26], and there is an unmet need for treatments that not only prolong survival but also maintain QoL in this patient population. In the FRESCO-2 study, fruquintinib improved survival versus placebo in patients with refractory mCRC [14], and in this pre-specified FRESCO-2 analysis, fruquintinib did not negatively impact HRQoL when compared with placebo. Patients receiving fruquintinib and placebo had a similar level of decline in HRQoL, as measured by LSM change from baseline scores of QLQ-C30 GHS and EQ-5D VAS, and based on pre-specified MIDs determining deterioration in QLQ-C30 and EQ-5D scores, fruquintinib versus placebo delayed median TTD in certain QLQ-C30 subscales (dyspnea, insomnia, and financial difficulty) and the EQ-5D VAS. A numerically greater proportion of patients who received fruquintinib versus placebo met the MID thresholds for stable and improved HRQoL (maximum post-baseline scores).

There is a need to understand the impact of different treatment options on the QoL of patients with mCRC to help inform treatment decisions. The results of this analysis contribute to the published data on the current treatment options. Other studies in the mCRC setting have conducted QoL analyses using similar QoL tools as in this analysis. The CORRECT study (NCT01103323), which assessed the efficacy and safety of regorafenib versus placebo in patients with mCRC (N = 760), reported no difference between treatment arms in patient-reported QoL at baseline or EOT, measured by QLQ-C30 and EQ-5D modules [27]. Similarly in SUNLIGHT (NCT04737187), a study of TAS-102 plus bevacizumab versus TAS-102 in patients with mCRC (N = 492), QoL was maintained in both arms when evaluated using QLQ-C30 and EQ-5D questionnaires [28]. QoL data are not available for TAS-102 from a placebo-controlled trial; however, the single-arm PRECONNECT study (NCT03306394) assessed QoL in a large patient cohort who had early access to TAS-102 (N = 793) [29]. In PRECONNECT, changes in QLQ-C30 GHS score were not deemed to be clinically relevant at any timepoint [29]. Our data support fruquintinib as an additional treatment option for refractory mCRC, demonstrating that active treatment can improve OS without negatively impacting patient QoL.

Deterioration in ECOG PS has been associated with a worsening of QLQ-C30 physical function scale scores and TTD to ECOG PS ≥ 2 may be a possible proxy measurement of QoL [30–33]. In this analysis, the proportion of patients with an ECOG PS of 0 in the fruquintinib arm was lower than in the placebo arm, likely due to a higher proportion of placebo-treated patients progressing earlier in FRESCO-2 than fruquintinib-treated patients [14], resulting in the remaining patients in the placebo arm being healthier and fitter than those who had progressed. Worsening of patient performance status was delayed with fruquintinib versus placebo, as shown by a longer TTD to ECOG PS ≥ 2 or death within 30+/−7 days after EOT (maximum of 37 days; (median 6.6 vs 2.9 months). A delay in deterioration of performance status has also been shown with TAS-102 in the phase 3 RECOURSE study (NCT01607957) in patients with mCRC (N = 800), where the median TTD to ECOG PS ≥ 2 was significantly longer versus placebo (5.7 vs 4.0 months; HR, 0.7; 95 % CI, 0.6–0.8; $P < 0.001$) [34]. As censoring

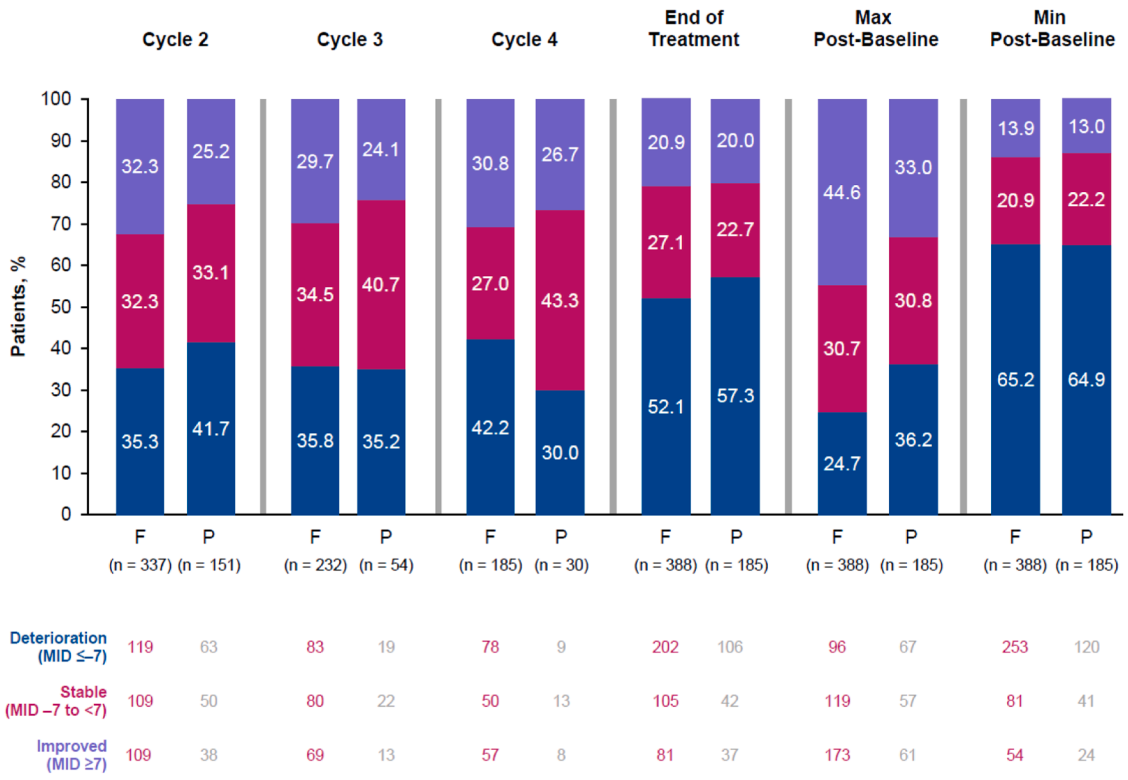


Fig. 3. Baseline and post-baseline assessment of patient health status according to EQ-5D-5L VAS scores (ITT population; fruquintinib n = 461, placebo n = 230). Percentages are based on the number of patients who received at least one dose of fruquintinib or placebo for the specific cycle (evaluable patients at each cycle from the ITT population). Percentages are based on n, the number of patients with a non-missing result for the given visit. The maximum post-baseline score represents the best condition during the treatment period; the minimum post-baseline score represents the worst condition during treatment. MID thresholds were as follows: deterioration MID ≤ -7, stable MID -7 to < 7, and improved MID ≥ 7 [18]. Abbreviations: EQ-5D-5L VAS, EuroQoL 5 Dimension 5 Level visual analog scale; F, fruquintinib; ITT, intent-to-treat; MID, minimally important difference; P, placebo.

methods may have differed between these studies and FRESCO-2, the findings should be interpreted with caution. Nonetheless, deterioration of ECOG PS is an important outcome in clinical trials to assess the impact of active treatment on patients' condition. This analysis of patients in FRESCO-2 showed that fruquintinib delayed deterioration of performance status, which was consistent with the QoL outcomes that were maintained over the course of treatment.

Results demonstrating that active treatments can maintain QoL without deterioration in the mCRC setting are encouraging. Furthermore, finding the optimal balance between prolonged survival and the quality of survival due to the toxicity of active agents is an important consideration in treatment decisions [35]. Studies of fruquintinib, including FRESCO-2, have demonstrated that it significantly improves survival while being well tolerated in patients with mCRC; indeed, in FRESCO-2, 48.9 % of patients treated with fruquintinib received ≥ 4 cycles, compared with only 14.8 % receiving placebo [14]. In FRESCO-2, the most frequent AEs of special interest related to fruquintinib included hypertension (28.9 %) and palmar-plantar erythrodysesthesia (18.6 %), with most events occurring in the first few cycles of treatment and then stabilizing at a lower rate in later cycles [36]. These AEs were managed with dose modifications, did not result in high incidences of discontinuations, and were consistent with the manageable safety profile of fruquintinib [14,36]. The quality-adjusted time without symptoms of disease or toxicity (Q-TWiST) analyses of FRESCO and FRESCO-2 both demonstrated that fruquintinib delayed disease progression and prolonged patient survival without substantially increasing toxicity compared with placebo [37,38]. It is important to note that patients receiving placebo in FRESCO and FRESCO-2 also experienced AEs, as the disease burden itself contributes to toxicity and impacts patient QoL [24–26]. These results, alongside the data from this HRQoL analysis demonstrate that the addition of active fruquintinib treatment in FRESCO-2 did not negatively impact QoL when compared with inactive placebo.

There were several limitations to this analysis: firstly, while the generic HRQoL instruments we used are robust, challenges exist around the complexity and length of questionnaires, and sensitivity and relevance for mCRC; additional analyses in patients with mCRC with CRC-specific questionnaires and scoring them alongside generic instruments would add to our understanding of the impact of treatments in mCRC [8]. The directional findings reported here showed no negative impact on patient QoL, and although statistical significance could not be reached, in part due to the *post-hoc* nature of some analyses, the results are supported by the FRESCO-2 Q-TWiST analysis, which is a well-established synthetic quality-adjusted life-year metric for the assessment of cancer treatments that can supplement patient-reported QoL data [38]. Secondly, in this study, QLQ-C30 and EQ-5D questionnaires were collected on day 1 of each 4-week treatment cycle, and as patients only received treatment up to day 21 (week 3) of each cycle, the 1-week treatment break before completing the questionnaires may have influenced how patients answered. However, although there was a treatment break, fruquintinib is eliminated slowly, resulting in high plasma exposure levels with target inhibition maintained for 5 days following the last dose. [11,39] Thirdly, as expected, patient numbers decreased over time, most commonly due to progressive disease [14], and a smaller sample size in later cycles may have impacted the conclusions that can be drawn from the data. The MMRM approach was used to analyze change in baseline QLQ-C30 and EQ-5D scores. This is a likelihood-based approach that assumes data are missing at random; as such, data that are missing at random in cases where an assessment was missed by a patient who continued on study (not due to death or

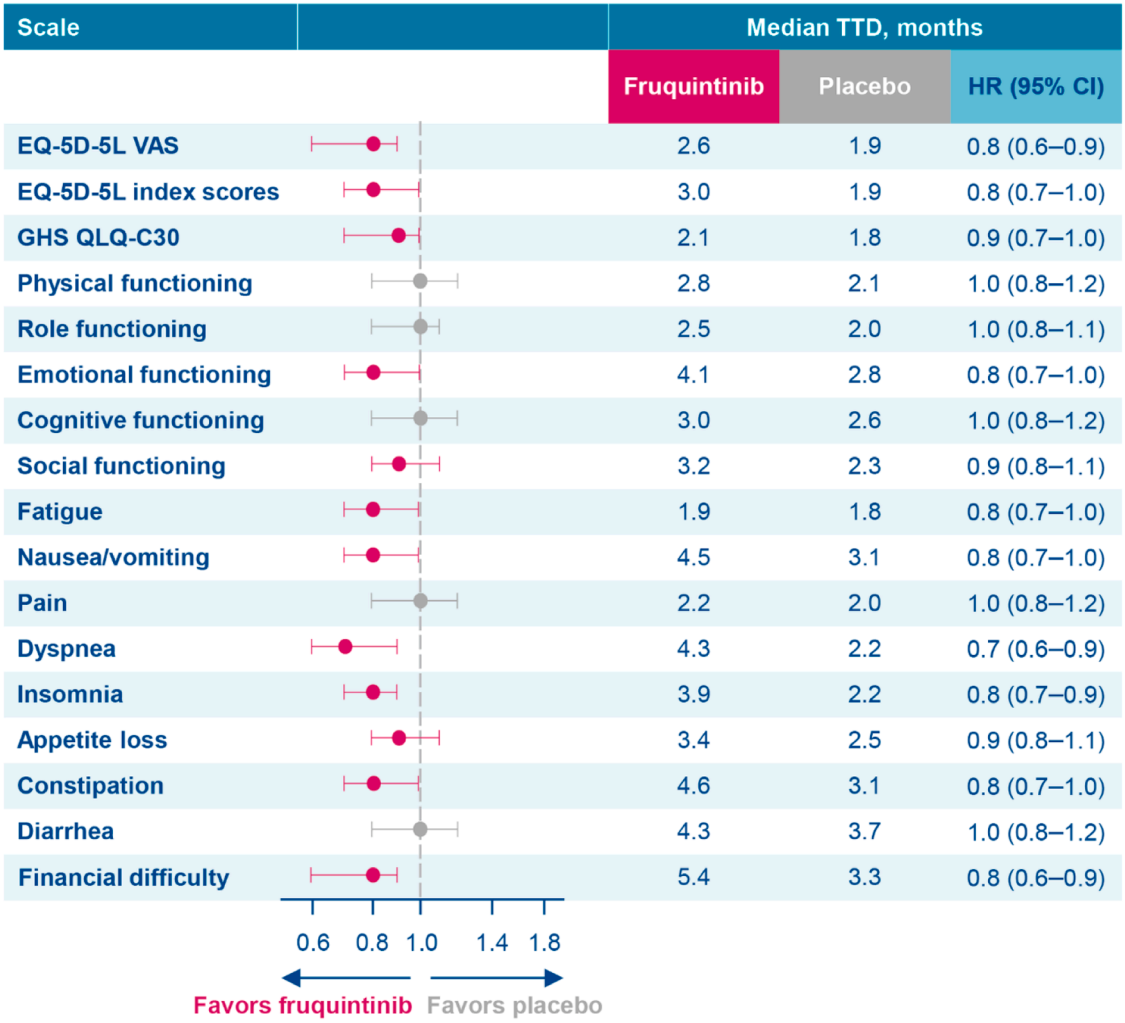


Fig. 4. Forest plot of TTD in patients receiving fruquintinib versus placebo according to QLQ-C30 GHS, QLQ-C30 sub-scales, and EQ-5D-5L scores (ITT population; fruquintinib n = 461, placebo n = 230). Median TTD (months) was calculated using the Kaplan–Meier method. Stratified HR and its 95 % CI were estimated using Cox hazard model (accounting for the stratification factors for randomization), in which treatment and baseline value of scale were included as fixed effects. TTD was based on predefined MIDs; these are listed in Supplementary Table 1 for each subscale. Abbreviations: CI, confidence interval; EQ-5D-5L VAS, EuroQoL 5 Dimension 5 Level visual analog scale; HR, hazard ratio; TTD, time to deterioration; QLQ-C30 GHS, Quality of Life Questionnaire Core 30 global health status.

treatment discontinuation) cannot be confirmed. Finally, TTD using MID thresholds for QLC-C30 and EQ-5D scores and TTD of ECOG PS were unplanned *post-hoc* analyses in the FRESCO-2 ITT population; therefore, the statistical comparisons are illustrative only as the study was not powered to assess a difference or to control for type I errors. Further, the data for whether a patient maintained the MID threshold for stable, improved, or deteriorated state at each follow-up assessment were not collected and so are only representative of the patients who met MID thresholds at each cycle. Identifying these limitations can help inform future studies in refractory mCRC and the development of QoL assessments. Despite these limitations, our findings contribute to the understanding of the impact of active treatment on patient HRQoL and can help to inform treatment decisions.

In conclusion, these results demonstrated that fruquintinib treatment delayed TTD of ECOG PS versus placebo and did not negatively impact HRQoL. These results, along with the improvement in survival and favorable toxicity profile, further support fruquintinib as a new treatment option for patients with refractory mCRC.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices, including the International Council for Harmonization. The protocol and amendments were approved by the institutional review board and independent ethics committee at each participating site. All patients provided written informed consent at enrollment.

Funding

This study was funded by HUTCHMED.

CRediT authorship contribution statement

Sobrero Alberto: Writing – review & editing, Validation, Supervision, Methodology, Investigation, Conceptualization. **Dasari Arvind**: Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Aquino Jeneth**: Writing – review & editing, Formal analysis, Conceptualization. **Lonardi Sara**: Writing – review & editing, Validation, Supervision, Resources, Investigation. **Garcia-Carbonero Rocio**: Writing – review & editing, Supervision, Resources, Investigation, Data curation, Conceptualization. **Elez Elena**: Writing – review & editing, Validation, Supervision, Resources, Investigation. **Yoshino Takayuki**: Writing – review & editing, Investigation. **Yao**

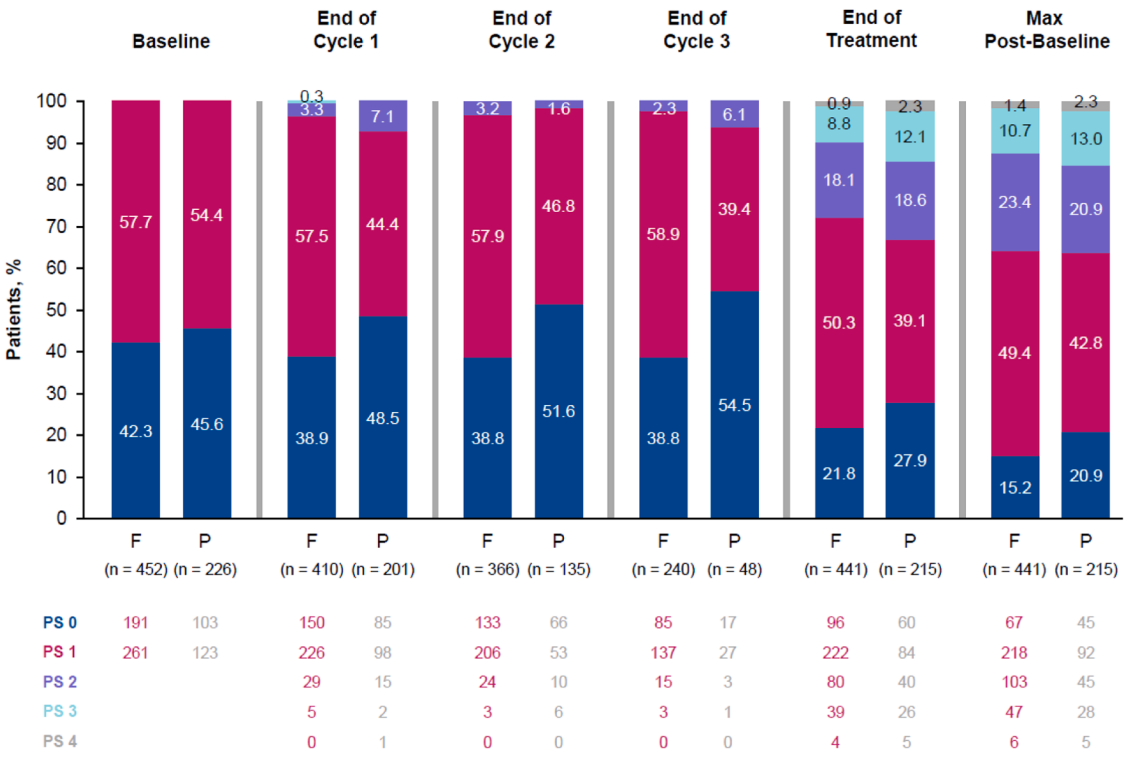


Fig. 5. Baseline and post-baseline assessment of patient ECOG PS (safety population; fruquintinib n = 456, placebo n = 230). Percentages are based on the number of patients who received at least one dose of fruquintinib or placebo for the specific cycle. The maximum post-baseline ECOG PS represents the worst condition during treatment. PS 0, Fully active, able to carry on all pre-disease performance without restriction; PS 1, Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; PS 2, Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50 % of waking hours; PS 3, Capable of only limited selfcare; confined to bed or chair more than 50 % of waking hours; PS 4, Completely disabled; cannot carry on any selfcare; totally confined to bed or chair. Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; F, fruquintinib; P, placebo.

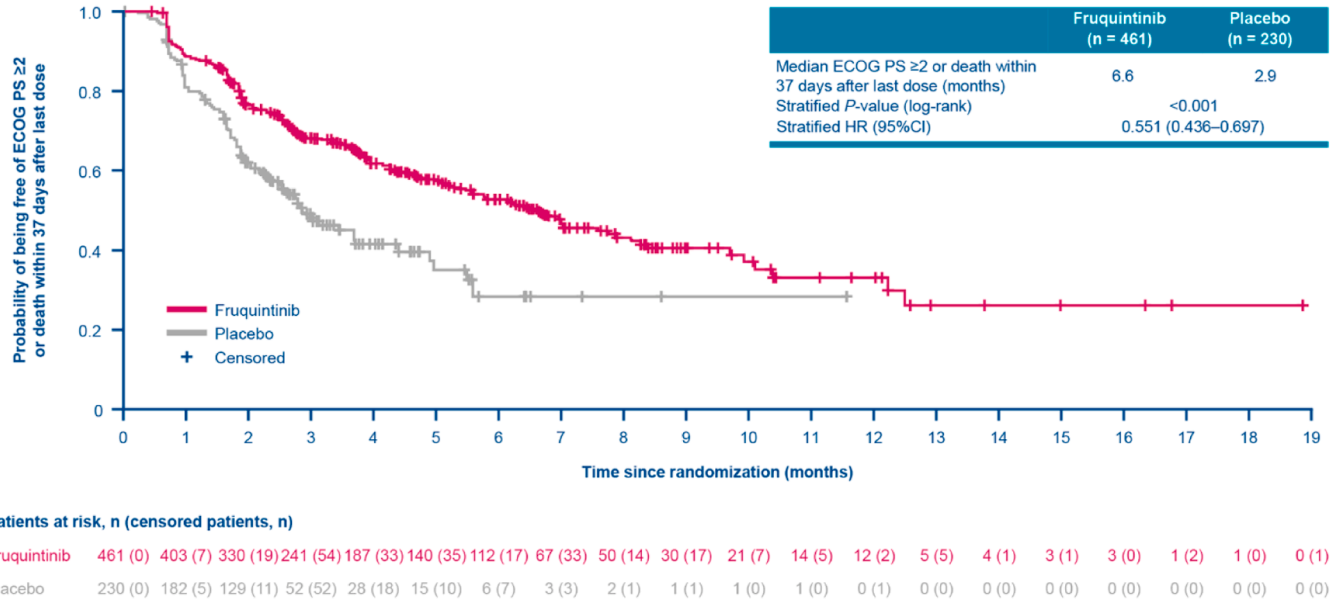


Fig. 6. TTD to ECOG PS ≥ 2 or death within 30+ /−7 days after EOT (ITT population; fruquintinib n = 461, placebo n = 230). Calculated as (date of death within 30+/−7 days after last dose date or first date of ECOG PS ≥2 – date of randomization + 1)/30.4375. Patients who did not have data post-randomization were censored at the date of randomization, and patients who had data post-randomization but had no ECOG PS ≥ 2 or no death within 30+ /−7 days after last dose date were censored at the date of last ECOG PS assessment date. Patients who died 30+ /−7 days after date of last dose were censored at the date of 30+ /−7 days after last dose. *P*-values are descriptive and should be interpreted with caution as this analysis was *post-hoc*. Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HR, hazard ratio; ITT, intent-to-treat; TTD, time to deterioration.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A. S. reports the ownership of stock/shares with Amgen; and an advisory council or committee position for and honoraria from Bayer, Servier, Bristol Myers Squibb (BMS), MSB, Glaxosmithkline (GSK), and Takeda. A.D. has received consulting fees from Eisai, Enterome, Guardant Health, HUTCHMED, Natera, Neogenomics, Personalis, Taiho, and Xencor; and grants or funds from BMS, Exelixis, Illumina, Lantheus, Personalis, Taiho, and Takeda. S.L. reports receiving honoraria (as invited speaker) from Roche, Eli Lilly, BMS, Servier, Merck Serono, Pierre Fabre, GSK, and Amgen; consulting fee (advisory boards) from Amgen, Astellas, Bayer, Merck Serono, Eli Lilly, AstraZeneca, Incyte, Daiichi-Sankyo, BMS, Servier, Merck Sharp & Dohme (MSD), GSK, Takeda, Rottapharm, and Beigene; as well as grants or funds (to institution) from Amgen, Merck Serono, Bayer, Roche, Eli Lilly, AstraZeneca, and BMS. R.G.C has received honoraria from AAA-Novartis, Advanz Pharma, Astellas, Bayer, BMS, Boerhinger Ingelheim, Esteve, GSK, HUTCHMED, Ipsen, Merck, Midatech Pharma, MSD, PharmaMar, Pierre Fabre, Roche, and Servier; and has received grants or funds from BMS, and MSD. E.E. has been on an advisory council or committee for, and has received honoraria as well as consulting fees from Agenus, Amgen, Bayer, BMS, Boehringer Ingelheim, Cureteq AG, GSK, Roche, Janssen, Lilly, Medscape, Merck Serono, MSD, Novartis, Organon, Pfizer, Pierre Fabre, Repare Therapeutics Inc., RIN Institute Inc., Sanofi, Seagen International, GmbH, Servier, and Takeda; has received grants or funds (to institution) from AbbVie Deutschland Gmbh & Co KG, Amgen Inc., Array Biopharma Inc., AstraZeneca Pharmaceuticals LP, Bayer, BeiGene, Bioncotech, Therapeutics, S.L., BioNtech RNA Pharmacuticals GMBH, BioNtech Small Molecules GMBH, Boehringer Ingelheim, Boehringer Ingelheim de España S.A., BMS International Corporation, Celgene International Sàrl, Daiichi Sankyo, Debiopharm International S.A., Genentech Inc., Gercor, HalioDX SAS, Roche, HUTCHMED, Iovance Biotherapeutics Inc., Janssen Research & Development, Janssen-Cilag S. A., MedImmune, Menarini, Menarini Ricerche SPA, Merck Health KGAA, Merck, Sharp & Dohme de España S.A., Merus NV, Mirati, Nouscom S.R.L., Novartis Farmacéutica S.A., Pfizer, PharmaMar S.A., Pledpharma A.B., Redx Pharma Plc, Sanofi Aventis Recherche & Développement, Scandion Oncology, Seattle Genetics Inc., Servier, Sotio A.S., Taiho Pharma USA Inc., Wntresearch AB and non-financial conflicts with American Society for Clinical Oncology (ASCO), Leadership Role, Member of the Scientific Program Committee and Developmental Therapeutics-Immunotherapy Track Leader, 2023–2024 term. European Society for Medical Oncology (ESMO), Member of the Scientific Committee 2024. ESMO, Speaker of the ESMO Academy. Sociedad Española de Oncología Médica (SEOM), Coordinator of the SEOM +MIR Section of Residents and Young Assistants. T.Y. declares receiving honoraria from Chugai Pharmaceutical, Takeda, Merck Biopharma, Bayer Yakuhin, Ono Pharmaceutical, and MSD K.K.; a consulting fee from Sumitomo Corp.; and grants or funds from Amgen, BMS, Chugai Pharmaceutical, Daiichi Sankyo, Eisai, FALCO biosystems, Genomedia, Medical & Biological Laboratories, Merus N.V., Molecular Health GmbH, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer Japan, Roche Diagnostics, Sanofi, Sysmex, Taiho Pharmaceutical, and Takeda. J.Y. reports consulting fees from HUTCHMED. A.S.B. has received consulting fees from Bayer, Pierre-Fabre, Servier, and Takeda. T.S. reports receiving honoraria from Eli-Lilly, Ono Pharmaceutical, BMS, and Daiichi-Sankyo; as well as grants or funds from Ono Pharmaceutical, BMS, Daiichi-Sankyo, and Shionogi Pharmaceutical. V.R. has received honoraria from Takeda. J.To. reports employment for Masaryk Memorial Cancer Institute, Brno, Czech Republic; receiving honoraria from Amgen, and Merck; and consulting fees from Merck. G.C. has held an advisory council or committee position for Regeneron, Takeda, and BMS; and reports research funding from HUTCHMED, Regeneron, BMS, AstraZeneca, Amgen, Roche, Bayer, Pharmacyclics, Incyte, Dizal Pharma, and Merck. T.P. has been on an advisory council or committee for Takeda, BMS, MSD, and Amgen. Z.Yu., A.G., and L.C. are employees of and hold stocks and shares with Takeda. Z.Ya., W.R.S., and M.K. are employees of and hold stocks and shares with HUTCHMED. J. Ta. reports the ownership of stock/shares with Oniria Therapeutics, Alentis Therapeutics, Pangaea Oncology, and 1TRIALSP; educational collaboration with Medscape Education, PeerView Institute for Medical Education, and Physicians Education Resource (PER); and has received consulting fees from Alentis Therapeutics, AstraZeneca, Aveo Oncology, Boehringer Ingelheim, Cardiff Oncology, CARSgen Therapeutics, Chugai, Daiichi Sankyo, Roche, Genentech Inc., hC Bioscience, Immodulon Therapeutics, Inspirna Inc., Lilly, Menarini, Merck Serono, Merus, MSD, Mirati, Neophore, Novartis, Ona Therapeutics, Ono Pharma USA, Orion Biotechnology, Peptomyc, Pfizer, Pierre Fabre, Samsung Bioepis, Sanofi, Scandion Oncology, Scorpion Therapeutics, Seattle Genetics, Servier, Sotio Biotech, Taiho, Takeda, and Tolremo Therapeutics. C.E. has been on an advisory council or committee for AbbVie, Amgen, GSK, IGM, Merck, Natera, Pfizer, Seagen, and Taiho. J.A., P.G.A., J.K., A.C.G., have no potential conflicts of interest to report.

Acknowledgments

The authors would like to thank all patients and their families, as well as all investigators for their valuable contributions to the FRESCO-2 study. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Philippa Lloyd, BSc, 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 (De Tora LM, et al. Ann Intern Med 2022;175:1298–304).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115268.

Data availability

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available from the completed study within 3 months from initial request, to researchers who provide a methodologically sound proposal. The data will be

provided after its de-identification, in compliance with applicable privacy laws, data protection and requirements for consent and anonymization.

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