NICE National Institute for Health and Care Excellence

NICE guidance

Fruquintinib for previously treated metastatic colorectal cancer

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Fruquintinib can be used as an option at third line or later to treat metastatic colorectal cancer in adults when previous treatment has included:

- fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without anti-vascular endothelial growth factor (VEGF) treatment, and
- anti-epidermal growth factor receptor (EGFR) treatment if the cancer is RAS wild-type, unless this was not suitable.

Fruquintinib can only be used if:

- trifluridine–tipiracil with bevacizumab is not suitable
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with fruquintinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop.

What this means in practice

Fruquintinib must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Fruquintinib must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that fruquintinib provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support implementation of this guidance.

Why the committee made these recommendations

Standard third-line treatment for metastatic colorectal cancer after chemotherapy (with or without anti-VEGF treatment) and anti-EGFR treatment is trifluridine–tipiracil with bevacizumab. When this is not suitable, treatment is trifluridine–tipiracil alone or regorafenib. Because most people will have had trifluridine–tipiracil at third line (either with bevacizumab or alone), regorafenib is more commonly used at fourth line.

Fruquintinib is not expected to replace trifluridine–tipiracil with bevacizumab. So for this evaluation, fruquintinib was considered only when trifluridine–tipiracil with bevacizumab is not suitable. This is narrower than the marketing authorisation.

Clinical trial evidence shows that fruquintinib increases how long people have before their cancer gets worse and how long they live, compared with placebo. Fruquintinib has not been directly compared in a clinical trial with regorafenib or trifluridine–tipiracil alone, but an indirect comparison suggests that it is likely to increase how long people have before their cancer gets worse.

There are some uncertainties in the economic model. But considering the condition's severity, and its effect on quality and length of life, the cost-effectiveness estimates are within the range NICE normally considers an acceptable use of NHS resources. So, fruquintinib can be used.

2 Information about fruquintinib

Marketing authorisation indication

2.1 Fruquintinib (Fruzaqla, Takeda) is indicated for 'the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy, and, if RAS wildtype and medically appropriate, an anti-EGFR therapy'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for fruquintinib.

Price

2.3 The list price of fruquintinib is £3,950.00 per 21-pack of 5-mg capsules and £790.00 per 21-pack of 1-mg capsules (excluding VAT; BNF online accessed June 2025).

2.4 The company has a commercial arrangement. This makes fruquintinib available to the NHS with a discount. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on the company's webpage on sustainability.

3 Committee discussion

The evaluation committee considered evidence submitted by Takeda, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of condition and impact on quality of life

3.1 Metastatic colorectal cancer (mCRC) is a tumour arising from the lining of the large intestine (colon and rectum) that has spread beyond the large intestine, most often to the liver, lungs or peritoneum. The patient experts noted that an mCRC diagnosis has a life-changing impact and that there are limited treatment options that prolong survival. They described the need for additional treatment options and that the side effects from existing treatments are problematic. These include pain, neuropathy and an inability to eat. Patient experts said that mCRC and the side effects from existing treatments affect the mental health of both the people with the condition and their family members. So, there is an unmet need for new treatments that are effective for this population. The committee agreed that there is an unmet need for people with mCRC.

Clinical management

3.2 The aim of treatment for mCRC is to prolong survival and improve quality of life. The treatment options for mCRC include:

- pembrolizumab (see NICE's technology appraisal guidance on pembrolizumab for untreated mCRC with high microsatellite instability or mismatch repair deficiency)
- cetuximab for epidermal growth factor receptor (EGFR)-expressing, RAS wild-type mCRC and panitumumab for RAS wild-type mCRC (see NICE's technology appraisal guidance on cetuximab and panitumumab for previously

untreated mCRC)

- encorafenib plus cetuximab (see NICE's technology appraisal guidance on encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive mCRC)
- nivolumab with ipilimumab (see NICE's technology appraisal guidance on nivolumab with ipilimumab for previously treated mCRC with high microsatellite instability or mismatch repair deficiency)
- trifluridine–tipiracil with bevacizumab (see NICE's technology appraisal guidance on trifluridine tipiracil with bevacizumab for treating mCRC after 2 systemic treatments; TA1008)
- trifluridine–tipiracil alone (see NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC; TA405)
- regorafenib (see NICE's technology appraisal guidance on regorafenib for previously treated mCRC; TA866)
- other chemotherapy for mCRC (see NICE's guideline on colorectal cancer)
- best supportive care.

The initial treatment choice depends on the presence or absence of 3 molecular markers: BRAF 600, RAS wild-type, and microsatellite instability or mismatch repair deficiency. When these molecular markers are present, specific biological medicines and chemotherapy are usually offered as first- and second-line treatments. In the absence of these molecular markers, treatment for mCRC consists of various combinations or sequences of chemotherapy agents including FOLFOX (folinic acid plus fluorouracil plus oxaliplatin), CAPOX (capecitabine plus oxaliplatin) and FOLFIRI (folinic acid plus fluorouracil plus irinotecan). For this evaluation, the company's submission positioned fruquintinib treatment for use at third line or later, in line with its marketing authorisation (see section 2.1). The clinical experts confirmed that the company's positioning represents how fruquintinib would be used in clinical practice. The committee acknowledged the clinical experts' perspective and concluded that fruquintinib would be used as a third-line or later treatment.

Comparators

3.3 The company's proposed comparators for fruquintinib matched the treatments listed in the original scope, that is trifluridine–tipiracil alone, regorafenib and best supportive care. At the first committee meeting, the clinical experts explained that most people would have regorafenib, trifluridine–tipiracil alone or fruquintinib, if available, as a third-line treatment. They also noted that a small proportion of people choose not to have treatment given the poor survival rate and burden associated with blood tests when having these treatments. The company highlighted that it expected fruquintinib to be offered primarily as a replacement for regorafenib. The committee noted that fruquintinib is unlikely to be offered to anyone for whom trifluridine–tipiracil alone or regorafenib is not suitable, so it thought that the comparison with best supportive care was less relevant. The committee also noted that, at the time of the first meeting, there was an ongoing appraisal that could affect the treatment pathway (see TA1008). The clinical experts said that there would be a quick uptake of trifluridine–tipiracil with bevacizumab if introduced. After the first committee meeting, trifluridine–tipiracil with bevacizumab was recommended for routine use for treating mCRC after 2 systemic treatments. In the company's response to the draft guidance consultation, it stated that most people would have trifluridine–tipiracil with bevacizumab at third line over alternative treatments. So, the company understood that fruquintinib would not be expected to replace trifluridine–tipiracil plus bevacizumab. Instead, it would be an option at third line for the minority of people who cannot have trifluridine–tipiracil plus bevacizumab, replacing regorafenib. The company explained that most fruquintinib use would be expected to be at fourth line as an alternative to regorafenib. It no longer considered trifluridine–tipiracil alone a relevant comparator at fourth line because most people would have had it with bevacizumab at third line. At the second committee meeting, the NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) said that 90% of people having third-line treatment have trifluridine–tipiracil with bevacizumab since its introduction into the NHS. The committee heard that fruquintinib could be appropriate at third line for people who cannot have or choose not to have trifluridine–tipiracil with bevacizumab because bevacizumab is an intravenous treatment often needing administration in hospital. The clinical experts explained that trifluridine–tipiracil with bevacizumab is well tolerated. But they said that regorafenib is increasingly rarely used at third line and often has side effects such as rashes and fatigue so usually

needs careful dose titration. They noted that fruquintinib would mostly be offered at fourth line as an alternative to regorafenib. It could also be an option for people otherwise choosing best supportive care because of the side effects associated with regorafenib. The patient expert explained the importance of having a choice of treatments available. They explained that some people may prefer treatments that can be taken at home rather than given in hospital. The committee considered that the relevant comparators should be what is used in NHS practice. It concluded that the relevant comparators at third line are trifluridine–tipiracil alone and regorafenib, and at fourth line are regorafenib and, to a lesser extent, best supportive care.

Clinical effectiveness

Key clinical trials: FRESCO and FRESCO-2

3.4 The clinical evidence for fruquintinib was from 2 randomised, double-blind, phase 3 clinical trials, FRESCO and FRESCO-2. These compared fruquintinib with placebo in adults with mCRC whose cancer had progressed after previous treatment. Previous treatments in FRESCO included chemotherapy, anti-vascular endothelial growth factor (VEGF) treatments and anti-EGFR treatments (see section 3.2). In addition to these treatments, FRESCO-2 included regorafenib and trifluridine–tipiracil as previous treatments. The primary outcome in the trials was overall survival. The results showed that fruquintinib offered statistically significantly better overall survival than placebo in both FRESCO (hazard ratio [HR] 0.65, 95% confidence interval [CI] 0.51 to 0.83) and FRESCO-2 (HR 0.66, 95% CI 0.55 to 0.80). The company pooled both datasets to get an overall-survival HR of 0.66 (95% CI 0.57 to 0.76), which was used for its clinical-effectiveness analyses. Progression-free survival was a secondary outcome in the clinical trials. Fruquintinib also offered statistically significantly better progression-free survival than placebo in FRESCO (HR 0.26, 95% CI 0.21 to 0.34), FRESCO-2 (HR 0.32, 95% CI 0.27 to 0.39) and the pooled analysis (HR 0.31, 95% CI 0.27 to 0.36). The committee concluded that fruquintinib offered better overall and progression-free survival than placebo.

Generalisability of trials

3.5 The company acknowledged differences in its clinical trials including previous treatment history and ethnicity. The FRESCO trial included only people in China, while FRESCO-2 was a global clinical trial that included people in the UK. In addition, around 30% of people in FRESCO had used an anti-VEGF treatment, compared with over 96% of people in FRESCO-2. NICE does not recommend anti-VEGF monotherapy (such as bevacizumab) for treating mCRC. The EAG noted that people in FRESCO were younger (about 55 compared with 62), had fewer previous treatments, and had been diagnosed with metastatic disease for a shorter length of time than people in FRESCO-2. The EAG did not consider ethnicity to be a treatment-effect modifier but noted that previous anti-VEGF treatment probably is. The EAG also said that none of the people in FRESCO had previously had treatment with trifluridine–tipiracil or regorafenib, whereas people in FRESCO-2 could previously have had these treatments. The committee recalled that the company pooled both trials in its modelling (see section 3.4) and was concerned that the differences in the trials might affect whether it was appropriate to do so. The clinical experts explained that because both trials had similar overall and progression-free survival results, they would not expect a difference in response to treatment. They explained that the clinical trial data suggested that the efficacy of fruquintinib was similar irrespective of previous treatment with anti-VEGF. The committee highlighted that the pooled data probably demonstrated the relative, but not the absolute, effect of fruquintinib. It concluded that the relative-effect estimates from the pooled trial data were reasonable for decision making in this case.

Network meta-analysis

3.6 The company did not have direct clinical-effectiveness evidence for fruquintinib compared with trifluridine–tipiracil alone or regorafenib. So, it did a network meta-analysis (NMA) to derive relative treatment-effectiveness estimates for overall and progression-free survival. For overall survival, there was no statistically significant difference between fruquintinib and trifluridine–tipiracil alone (HR 0.95, 95% CI 0.78 to 1.15) or regorafenib (HR 0.93, 95% CI 0.75 to 1.16). Fruquintinib significantly improved progression-free survival compared with trifluridine–tipiracil alone (HR 0.67, 95% CI 0.55 to 0.80) and regorafenib (HR 0.66

95% CI 0.54 to 0.81). The company did additional analyses on the potential treatment modifiers, including previous anti-VEGF treatment and ethnicity. The results were broadly similar to the overall NMA results, except for the overall survival of people who had not had anti-VEGF treatment, in which regorafenib showed better overall survival than fruquintinib. The EAG noted that the results from the subgroup of people who had not had anti-VEGF treatment should be interpreted with caution because of the small population numbers informing the analysis. The committee noted the discrepancy between the overall-survival and the progression-free survival results. It was concerned that the improvement shown by fruquintinib did not translate into better overall survival. The clinical experts could not fully address the committee's concerns but noted the importance of each new treatment providing additive survival benefit for people with mCRC. The company explained that it had not assessed the differences in post-progression treatments in all trials. But in its economic model it had done a probabilistic sensitivity analysis to assess the uncertainty in the NMA results. The committee noted that the NMA assumed that the proportional hazards assumption held (see section 3.8). It concluded that there was uncertainty in the company's NMA results, and it was concerned that this could affect the progression-free survival extrapolation (see section 3.10).

After draft guidance consultation the company argued that while both progression-free survival and overall survival are important outcomes, progression-free survival and quality of life are the most important outcomes in this population. It explained that the NMA shows a significant improvement in progression-free survival and that FRESCO-2 demonstrates that quality of life is not negatively impacted by treatment with fruquintinib. At the second meeting, the clinical experts explained that in a third-line setting, progression-free survival is the most important outcome but that at later lines overall survival becomes more important. The committee concluded that both outcomes are important.

Economic model

Company's modelling approach

3.7 The company used a 3-state (progression-free, post-progression and death)

partitioned survival model to estimate the cost effectiveness of fruquintinib. The model took the perspective of the NHS and personal social services. It had a time horizon of 10 years, a weekly cycle length, and discounted costs and quality-adjusted life years (QALYs) at a rate of 3.5% per year. The committee concluded that the company's model was appropriate for decision making.

Overall survival extrapolation

3.8 In its original base case, the company estimated long-term overall survival for fruquintinib and best supportive care by jointly fitting parametric models to the pooled FRESCO and FRESCO-2 overall-survival data. It applied the generalised gamma model to its base case because this provided good visual and statistical fit and was clinically validated. To extrapolate regorafenib and trifluridine–tipiracil alone overall survival, the company applied the hazard ratios from its NMA to the extrapolated fruquintinib curves. The EAG raised concerns about the company's approach. It argued that using jointly fitted parametric models was flawed because the results of the company's global test for proportional hazards assumption was statistically significant; that is, it suggested that the proportional hazards assumption was not fully met. The EAG preferred to fit the survival models individually for fruquintinib (log-normal) and best supportive care (log-logistic). Full overall-survival data for regorafenib and trifluridine–tipiracil alone was not publicly available. To extrapolate overall survival for these treatments, the EAG used digitised Kaplan–Meier curves from the trials for regorafenib (CORRECT) and trifluridine–tipiracil alone (RECOURSE and Yoshino et al. [2023]), which it sourced from the literature. It then fitted independent survival models (generalised gamma distribution) to these. The EAG acknowledged that its approach relied on naive comparison across trials, but noted that it was not appropriate to fit hazard ratios to the accelerated failure time models used by the company. The committee in this case was concerned, not about fitting hazard ratios to accelerated time function models but about the proportional hazards assumption not holding for overall survival. It asked the company if it had explored the log-time interaction for each treatment to quantify the uncertainty in the proportional hazards. The company explained that it had not done this analysis. The committee highlighted that although applying NMA hazard ratios to the company's models was not ideal, this maintained randomisation in the clinical trials. So, it preferred this approach to the individually fitted curves, which relied

on naive comparisons across trials. Specifically, the committee noted that its preferred method for survival extrapolation was to apply the NMA hazard ratios for each treatment to real-world evidence (see section 3.9). But it concluded that further analysis was needed to assess whether the proportional hazards assumption was appropriate. It said that, if this could not be done, the company should explore alternative approaches that relax the proportional hazards assumption (such as fractional polynomials or piecewise approaches). It said that only then could the NMA hazard ratios be plausibly applied.

At draft guidance consultation the company noted that there were limitations with the interaction tests of time and log-time requested by the committee. It considered that these reduced the suitability to assess the proportional hazards assumption, such as the risk of overfitting to the data and using studies that were underpowered for use in these tests. The company provided additional tests to assess the proportional hazards assumption. It compared fruquintinib with trifluridine–tipiracil alone and regorafenib using log-cumulative hazard plot inspections, global test of Schoenfeld residuals and interaction tests with time and log-time. The EAG explained that there was still uncertainty around whether the proportional hazards assumption held true. The committee noted there was no further analysis provided around the proportionality observed in the randomised trial data. The committee explained that it would like to see interaction tests with time and log-time for fruquintinib compared with best supportive care to assess whether the proportional hazards assumption within the NMA is reasonable. The committee concluded that if the proportional hazards assumption did not hold for overall survival, it would like to see time-varying modelling to further explore the impact of the assumption.

After the second committee meeting the company provided its analysis of the interaction between treatment and time on treatment and log-time for fruquintinib compared with best supportive care. The analysis used pooled data from the FRESCO and FRESCO-2 trials. The results of the analysis suggested that the assumption of proportional hazards did not hold for overall or progression-free survival. Based on this the company also provided a fractional polynomial NMA to explore the impact of uncertainty but noted that there was crossing of curves between treatments, which inferred that this method was not clinically plausible. It explained that the model may underestimate clinical expert estimates of survival time. So in its base case the company capped hazard ratios at 1 to

prevent curves crossing and generate more plausible estimates. The EAG agreed that it was reasonable to use capping in the fractional polynomial NMA. It noted that the impact on the results with capping applied compared to the original NMA was small. The committee concluded that it was satisfied with the company's updated analysis.

Overall survival using SACT data

3.9 In a recent NICE evaluation on mCRC, the committee requested additional analyses using real-world evidence in the NHS for trifluridine–tipiracil alone to resolve uncertainty in overall-survival modelling (see TA1008). For this evaluation, the EAG did a similar analysis by:

- applying a parametric model (the best-fitting models were generalised gamma and log-logistic) to Systemic Anti-Cancer Therapy (SACT) data for trifluridine–tipiracil alone
- using the extrapolated trifluridine–tipiracil alone curve as the reference curve
- applying the NMA hazard ratios (see section 3.6) for fruquintinib, regorafenib and best supportive care to the reference curve to derive overall-survival estimates.

The committee noted that the log-logistic curve suggested that a small proportion of people having fruquintinib would be alive after 10 years and would benefit from fruquintinib indefinitely. The EAG explained that it preferred the generalised gamma curve because this provided more plausible estimates. It also highlighted that a treatment-effect waning assumption might be needed if the log-logistic curve were applied. The committee asked the clinical experts if they would expect people to be alive 10 years after treatment. The clinical expert explained that, in their practice, with a cohort of about 100 people, 1 person remained alive after 5 years. So, people for whom treatment works exceptionally well may be alive after 10 years. The experts noted that the impact of disease biomarkers (see section 3.2) on people's treatment response was not captured in the SACT data, and that this could affect the overall-survival results. The committee did not settle on either the generalised gamma or the log-logistic model. So, it said that it

would also like to see cost-effectiveness estimates based on an average of both models for its decision making. At the first committee meeting, the committee concluded that it preferred using the real-world evidence (SACT data) for modelling overall survival for trifluridine–tipiracil alone. This was because this reflected the expected absolute survival for the relevant population.

At draft guidance consultation, the company updated its model as requested by the committee. But it noted some limitations with using the SACT overall-survival data. This included the lack of baseline characteristics for the population included in the dataset, and the lack of data for progression-free survival, adverse events, subsequent treatments and time to treatment discontinuation. The company stated that this affects the ability to assess how similar the SACT data population is to the relevant trial populations. But it acknowledged that overall-survival outcomes from the SACT data and the key trials for trifluridine–tipiracil alone were similar. The committee was satisfied that the updated analysis was appropriate for a third-line population if further analysis demonstrated that the proportional hazards assumption held (see section 3.8). But it noted that at fourth line, regorafenib is the most relevant comparator. So, it wanted to see further analyses using the SACT data for regorafenib for the fourth-line population. In its updated analysis the company used a fractional polynomial NMA with capping applied because the proportional hazards assumption did not appear to hold (see section 3.8).

After the second committee meeting the company was unable to obtain SACT data for regorafenib within a reasonable timeframe and used a fourth-line scenario with fruquintinib as the reference curve based on the FRESCO-2 trial data. The committee agreed that in the absence of the SACT data for regorafenib this approach was appropriate. The committee said that it preferred using the real-world evidence (SACT data) for modelling overall survival for trifluridine–tipiracil alone (at third line) and regorafenib (at fourth line) because this reflected the expected absolute survival for the relevant populations. But the committee concluded that the approach taken by the company was acceptable.

Progression-free survival extrapolation

3.10 The company modelled progression-free survival with the same approach used for overall survival in its submission (see section 3.8). That is, it applied jointly fitted parametric models (log-normal) for fruquintinib and best supportive care. For regorafenib and trifluridine–tipiracil alone, it applied the NMA hazard ratios to the fruquintinib extrapolation. The EAG reiterated its concerns about the company's survival modelling approach (see section 3.8). That is, the global test did not support proportional hazards for progression-free survival. It highlighted that the company's progression-free survival estimate for trifluridine–tipiracil alone was substantially higher than the clinical trial results. It also noted that visual assessments of the relevant plots for evaluating the proportional hazards assumption did not support its use for progression-free survival. The EAG preferred to apply independently fitted curves for fruquintinib (log-normal) and best supportive care (log-logistic). It also applied independently fitted log-normal models to digitised Kaplan–Meier curves from the regorafenib (CORRECT) and trifluridine–tipiracil alone (RECOURSE and Yoshino et al. 2023) trials. The committee had the same concerns as with the overall-survival extrapolation (see section 3.8). It noted that the EAG's approach would not preserve randomisation. The committee would have preferred to use trifluridine–tipiracil alone progression-free survival trial data, which is generalisable to the NHS, as a reference curve. It would then prefer to apply the NMA hazard ratios to estimate progression-free survival for all other treatments. But it was not convinced that the proportional hazards assumption held for progression-free survival. It concluded that a further analysis of log-time interaction for each treatment was needed to assess if the proportional hazards assumption held. It said that, if it did not hold, alternative approaches that relax the proportional hazards assumption (such as fractional polynomials or piecewise approaches) should be explored.

At draft guidance consultation the company updated its model to use trifluridine–tipiracil alone as the reference curve and provided further analyses of proportional hazards. It noted that there were limitations with the interaction tests with log-time that were requested by the committee and did additional testing of proportional hazards (see section 3.8). The committee noted that, as with overall survival, there was no further analysis provided around the proportionality observed in the randomised trial data. The committee explained that it would like to see interaction tests with time and log-time for fruquintinib

compared with best supportive care to assess whether the proportional hazards assumption within the NMA is reasonable. The committee was satisfied with the approach to modelling progression-free survival (with trifluridine–tipiracil alone as the reference curve) for the third-line population should proportional hazards be demonstrated to hold. But it noted that at fourth line, regorafenib is the most relevant comparator. So, it wanted to see progression-free survival trial data for regorafenib, which is generalisable to the NHS, as a reference curve. It then wanted the NMA hazard ratios to be applied to estimate progression-free survival for fruquintinib and best supportive care assuming that proportional hazards was demonstrated to hold.

After the second committee meeting the company did a fractional polynomial NMA and applied capping to prevent the curves crossing. The company preferred to use a reference curve for third-line treatment based on pooled data from RECOURSE and Yoshino et al. (trifluridine–tipiracil alone) for progression-free survival. It presented scenarios for the fourth-line treatment setting using either regorafenib (from CORRECT) or fruquintinib (from FRESCO-2) as the reference curves. The company preferred to use FRESCO-2 data, which was in a fourth-line population, as the reference curve in its updated base case. It preferred to do this because it considered that the results using the CORRECT trial data lacked face validity (that is, the results were unexpected). The EAG agreed with the concerns about using the CORRECT regorafenib curve as the reference curve but noted that both approaches were plausible. The committee concluded that it was satisfied with the company's updated analysis using a reference curve based on FRESCO-2 data.

Time to treatment discontinuation

3.11 The company initially modelled time to treatment discontinuation for fruquintinib by fitting a log-normal parametric curve to the pooled FRESCO and FRESCO-2 time to treatment discontinuation data for fruquintinib. The EAG preferred a generalised gamma curve because this better reflected the idea that fewer people would have treatment at the tail end of the curve. For regorafenib and trifluridine–tipiracil alone the company modelled time to treatment discontinuation by applying the progression-free survival hazard ratios from the NMA of these treatments to the fruquintinib time to treatment discontinuation curves. The

company took this approach because data for regorafenib and trifluridine–tipiracil alone was not publicly available. The EAG had concerns about the company's approach because it assumed that treatment discontinuation was proportional between treatments and constant over time. It highlighted that this was unlikely because the treatments have different adverse event profiles. Regorafenib, in particular, would probably have a higher initial discontinuation rate than the other treatments. The EAG preferred estimates from the log-normal model applied to digitised time to treatment discontinuation data (from RECOURSE and Yoshino et al. 2023) for trifluridine–tipiracil alone. The same time to discontinuation data was not publicly available for regorafenib, so the EAG applied an exponential model to the median time to discontinuation reported in the CORRECT trial. The EAG also did an additional analysis, which assumed that only a proportion of people in the progression-free health state would have regorafenib. It estimated the proportion by dividing the mean time on treatment in CORRECT by the mean modelled progression-free survival estimated for regorafenib using the company's model. The committee highlighted that clinical trial data should be used when available and plausible. It concluded at the first meeting that applying a log-normal curve to the digitised trial time to treatment discontinuation data for trifluridine–tipiracil alone and an exponential curve to the median time on treatment for regorafenib was not ideal but reasonable. It also concluded that a generalised gamma curve should be used to model treatment discontinuation for fruquintinib. In its response to the draft guidance consultation the company highlighted the limitations of the committee's preferred approach of estimating time to treatment discontinuation for regorafenib and trifluridine–tipiracil alone but updated its base case to align to the committee's preferred approach. After consultation, the company and EAG agreed that a generalised gamma curve should be used to model treatment discontinuation for fruquintinib. The committee concluded that it was satisfied with the company's updated approach.

Relative dose intensity

3.12 The company assumed that fruquintinib, regorafenib and trifluridine–tipiracil alone have equal relative dose intensity. It argued that treatment-specific relative dose intensities reported in the trials differed only because of different definitions of relative dose intensity across the trials. So, in its base case, it applied the fruquintinib relative dose intensity from the pooled FRESCO and FRESCO-2 trials

for these treatments (89.6%). The EAG acknowledged that there might be inconsistencies in the definitions of relative dose intensity. But it preferred to use treatment-specific estimates from the regorafenib (78.9%) and trifluridine–tipiracil alone (89.0%) trials to be consistent with the source of efficacy estimates used in the company's model. The committee asked the clinical experts whether these treatments were likely to have the same relative dose intensities. The experts explained that regorafenib would be expected to have a lower relative dose intensity because of its toxicity profile. They noted that they would usually start treatment with regorafenib at a lower dose, then slowly increase the dose until the person's toxicity profile was stable. If needed, the dose could be reduced. The Cancer Drugs Fund lead explained that reducing the dose of regorafenib and trifluridine–tipiracil alone reduced the acquisition cost of the drugs. But for fruquintinib the acquisition cost would be reduced only if a dose of 3 mg per day is prescribed. The committee acknowledged the clinical experts' opinion and concluded that the trial-specific relative dose intensities should be applied and that the acquisition cost of fruquintinib should be accurately modelled.

In its response to draft guidance consultation the company updated its pricing of fruquintinib and accurately modelled this. But it maintained its approach of using the relative dose intensity from FRESCO and FRESCO-2 for all treatments. This is because it did not consider the definitions of relative dose intensity used across the different trials to be comparable. It also recalled clinical expert input from its advisory board. This suggested that a lower relative dose intensity would be expected for regorafenib than fruquintinib but not as low as the values from CORRECT suggest. The EAG acknowledged the uncertainty but kept the assumption of treatment-specific relative dose intensity in its base case. The committee heard the concerns raised by the company and the EAG and acknowledged that the relative dose intensity for regorafenib may have been impacted by the definition in the trial. It considered that a further analysis applying the same definition of relative dose intensity from CORRECT for regorafenib to the fruquintinib data could be done so that a consistent definition is used. It explained that the ratio from this could be used to increase the relative dose intensity of regorafenib accordingly. The committee further concluded that trial-specific values should be used for fruquintinib and trifluridine–tipiracil alone. The company updated its base case to align with the EAG-preferred base case and the committee-preferred assumptions of using trial-specific relative dose intensity for fruquintinib, regorafenib and trifluridine- tipiracil. The committee

concluded that it was satisfied with the company's updated analysis.

Subsequent treatment

3.13 The company's original base case used pooled FRESCO and FRESCO-2 data to inform the modelling of subsequent treatment. It also assumed that people would have subsequent treatment for only 1 week because of the poor survival rates associated with mCRC. The company provided a scenario analysis in which treatments not recommended by NICE for mCRC (such as bevacizumab monotherapy) were excluded, and the list of subsequent treatments was reweighted accordingly. The EAG used the company's scenario analysis for its base case but instead applied a duration of 8 weeks, based on clinical advice. The committee considered additional analysis done by the EAG, which used NHS England data. This showed that 35% of people who have regorafenib or trifluridine–tipiracil alone would have post-progression treatment. The Cancer Drugs Fund lead explained that it was unclear if this figure represented all people having treatment across the NHS, including people having treatment within the Cancer Drugs Fund. The committee recalled clinical expert opinion that each new treatment provided additive benefit (see section 3.6) and noted that a post-progression treatment duration of 1 week was unlikely to be plausible. It concluded that the NHS England data on the number of people having post-progression treatment should be applied with an 8-week treatment duration considering only those treatments used in the NHS. After draft guidance consultation, the company agreed to accept the committee's preferred approach and updated its base case to use the:

- distributions for subsequent treatments based on clinical expert opinion, and
- NHS England estimates for the proportion of people having regorafenib or trifluridine–tipiracil alone for 8 weeks.

The committee concluded that it was satisfied with the updated analysis.

Utility values

3.14 The utility values used in the company's original base case were from EQ-5D-3L

data collected in the FRESCO-2 trial. The company fitted a regression model to the data and adjusted for age and sex. It did not model treatment-specific utility values. The company's utility values were based on health state: 0.71 for progression free and 0.65 for post-progression. The committee also considered that the following utility values from previous and ongoing NICE evaluations were relevant:

- trifluridine–tipiracil alone (CORRECT trial; TA405): pre-progression 0.73, post-progression 0.59
- regorafenib (CONCUR and CORRECT trials; TA866): pre-progression 0.72, post-progression 0.59
- trifluridine–tipiracil with bevacizumab (SUNLIGHT trial; TA1008): pre-progression 0.76, post-progression 0.68.

The EAG noted that the company's base-case post-progression utility value appeared high compared with other appraisals (TA405 and TA866) and could lack face validity. It also noted that the utility values were sourced from FRESCO-2, whereas the clinical-effectiveness data was from the pooled trial results. The committee was concerned that the utility values were from a population that did not fully represent the pooled FRESCO and FRESCO-2 populations used for the clinical-effectiveness estimates in the economic model. The committee thought that pooling all the available utility values would have provided useful additional data for decision making. But in the absence of this it said that the CORRECT trial utility values were likely to be a plausible approximation of the pooled estimate. The committee concluded that it would like to see further analyses using the CORRECT trial utility values, and the pooled estimate of all the relevant utility values.

After draft guidance consultation the company accepted the committee's preferred approach of using the utility values from the CORRECT trial in its base case. It also explored the impact of using pooled utility data from different sources in a scenario analysis, informed by a meta-analysis (pre-progression 0.72, post-progression 0.64 in a fixed-effects model). The EAG agreed with the company's approach to pooling the utility values in the scenario analysis, noting that the fixed-effects and random-effects models produced similar results. But it had concerns that the utility values from the

SUNLIGHT trial (trifluridine–tipiracil with bevacizumab) were significantly higher than values from other appraisals, particularly for people with progressed mCRC. It thought that the pooled values were reasonable but with some uncertainty. At the second committee meeting, the committee considered that the most relevant utility values at third and fourth line may differ. The clinical experts confirmed that the FRESCO-2 values, specific to a fourth-line population, may be most relevant in that setting. The committee maintained its view from the first meeting, that the pooled values were most relevant in the third-line population. The committee concluded that the pooled utility values from the fixed-effects meta-analysis should be used for the third-line population and the FRESCO-2 utility values should be used for the fourth-line population.

Severity

3.15 The committee may apply a greater weight (a severity modifier) to QALYs if technologies are indicated for conditions with a high degree of severity. The committee considered the severity of mCRC (the future health lost by people living with the condition and having standard care in NHS). It understood, at the first meeting, that in the company and EAG base cases, the QALYs generated implied a QALY weighting of 1.7 for best supportive care, regorafenib and trifluridine–tipiracil alone. It recalled the EAG's perspective about people in FRESCO being younger than people in FRESCO-2 (see section 3.5). The committee considered 2 additional severity weighting analyses:

- using FRESCO-2 data as the source of clinical input and baseline characteristics
- using the trifluridine–tipiracil alone SACT data to estimate mean age (65 years) and to model overall survival (see section 3.9).

Both analyses generated slightly different QALYs from the company and the EAG base cases, but the severity weighting remained at 1.7. The committee considered that using the SACT dataset to inform the severity weighting decision was preferable. But it concluded that it would re-examine the appropriate QALY weighting to be applied after the additional analysis to

resolve uncertainty related to survival extrapolation had been done. It would do this using its preferred source for utility values (see section 3.8 and section 3.14).

After the draft guidance consultation, the company maintained its stance that a mean starting age of 65 as suggested from the SACT dataset would overestimate the mean age of people eligible for fruquintinib in NHS practice. It also highlighted that the SACT dataset may over represent third-line treatment because most fruquintinib use is expected to be in the fourth-line setting. It explained that people going on to have active treatment at fourth line may be younger. The EAG preferred to maintain the same starting age as the SACT dataset in its base case as well as the overall-survival curves from the SACT dataset for calculating severity weightings for use in the economic model. At the second committee meeting, the Cancer Drugs Fund lead advised that the mean starting age from the SACT dataset for people having trifluridine–tipiracil with bevacizumab at third line was 64.3 years while the mean age of people having regorafenib at fourth line was 64.7 years. The committee preferred to use the starting ages for third-line and fourth-line treatment from the SACT dataset for calculating severity weightings because they are representative of the population that could have fruquintinib. It concluded that the mean starting age from the SACT dataset was appropriate for decision making. After the second committee meeting the company updated its severity modifier calculations to align with the committee preference for using the SACT dataset starting age. The committee concluded that a 1.7 severity modifier was appropriate for decision making.

Other factors

Equality

3.16 No equality concerns were raised by the stakeholders. The committee did not consider that there were any equality issues that would have an impact on its decision making.

Cost-effectiveness estimates

Acceptable ICER

3.17 NICE's health technology evaluations manual notes that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the uncertainty in the company's clinical evidence and economic model assumptions. The committee acknowledged that there is an unmet need for people with mCRC. It also flagged that the benefit of fruquintinib being easier to tolerate than regorafenib may not be fully captured within the model. Weighing up the uncertainty in the evidence and the uncaptured benefit, the committee considered that an acceptable ICER would be in the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

Company and EAG cost-effectiveness estimates

3.18 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for fruquintinib, regorafenib and trifluridine–tipiracil alone. With a 1.7 QALY weighting applied for severity, both the company's and EAG's base-case ICERs were within the range that NICE normally considers an acceptable use of NHS resources. The committee's preferred assumptions were:

- to use the following comparators:
  - regorafenib and trifluridine–tipiracil alone at third line
  - regorafenib and best supportive care at fourth line
- to use the capped fractional polynomial NMA to generate hazard ratios for overall and progression-free survival (see section 3.8)
- for the overall-survival reference curves (see section 3.9):

  - to use SACT data for trifluridine–tipiracil alone at third line
  - in the absence of the regorafenib fourth-line data to use the fourth-line FRESCO-2 fruquintinib data
- to use the following progression-free survival reference curves (see section 3.10):
  - RECOURSE and Yoshino et al. (trifluridine–tipiracil alone) at third line
  - FRESCO-2 (fruquintinib) at fourth line
- to apply:
  - a log-normal curve to the digitised trial data for trifluridine–tipiracil alone to estimate time to treatment discontinuation
  - an exponential curve for regorafenib that passes through the reported median time on treatment, and a generalised gamma curve for fruquintinib to estimate median time on treatment (see section 3.11)
- to use trial-specific relative dose intensity for fruquintinib, trifluridine–tipiracil alone and regorafenib (see section 3.12)
- use NHS England estimates of subsequent treatment (35%) and a duration of 8 weeks with only treatments used in the NHS (see section 3.13)
- to use:
  - the pooled fixed-effects estimate of all the relevant utility values in the third-line population
  - FRESCO-2 utility values in the fourth-line population (see section 3.14).
- to use the mean starting age from the SACT dataset to inform the severity weighting estimates (see section 3.15); these are a mean starting age of:
  - 64.3 years for trifluridine–tipiracil with bevacizumab at third line
  - 64.7 years for regorafenib at fourth line.

Conclusion

Recommendation

3.19 Using the committee's preferred assumptions, and an updated confidential patient access-scheme discount, the ICER was within the range that NICE considers a cost-effective use of NHS resources. So, fruquintinib can be used in the NHS.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The NHS England Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated metastatic colorectal cancer and the healthcare professional responsible for their care thinks that fruquintinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley and Baljit Singh
Chair and vice chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Raphael Egbu and Emma Bajela
Technical leads

Michelle Green
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Vonda Murray
Project manager

Richard Diaz
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