NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Fruquintinib for previously treated metastatic colorectal cancer

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using fruquintinib in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using fruquintinib in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 29 October 2024
- Second evaluation committee meeting: 12 December 2024
- Details of membership of the evaluation committee are given in section 4.

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1 Recommendations

1.1 Fruquintinib is not recommended, within its marketing authorisation, for treating metastatic colorectal cancer in adults who have had previous treatment, including:

- fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-vascular endothelial growth factor [VEGF] treatment, and
- if the cancer is RAS wildtype, an anti-epidermal growth factor receptor [EGFR] treatment if that is appropriate.

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.

Why the committee made these recommendations

Standard treatment for metastatic colorectal cancer after treatment with chemotherapy (with or without anti-VEGF treatment) and anti-EGFR treatment includes regorafenib and trifluridine–tipiracil.

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 standard treatment, but an indirect comparison suggests that there is no difference in how long people live with any of these treatments.

There are uncertainties in the economic model. This is because of the method used to estimate how long people live. The cost-effectiveness estimates are unlikely to be within the range NICE normally considers a cost-effective use of NHS resources,

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and further analysis is needed to resolve the uncertainties. So, fruquintinib is not recommended.

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 will be available in the summary of product characteristics for fruquintinib.

Price

2.3 The list price of fruquintinib is confidential until the final guidance is published.

2.4 The company has a commercial arrangement, which would have applied if fruquintinib had been recommended.

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

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intestine, most often to the liver, lung or peritoneum. The clinical experts confirmed statements from patient experts, which noted that mCRC has a life-changing impact on people diagnosed and that there are limited treatment options that prolong survival. 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:

- nivolumab plus ipilimumab (see NICE's technology appraisal guidance on nivolumab with ipilimumab for previously treated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency)
- pembrolizumab (see NICE's technology appraisal guidance on pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency)
- encorafenib plus cetuximab (see NICE's technology appraisal guidance on encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer)
- cetuximab for epidermal growth factor receptor-expressing, RAS wild-type mCRC (see NICE's technology appraisal guidance on cetuximab and panitumumab for previously untreated metastatic colorectal cancer)
- panitumumab for RAS wild-type mCRC (see NICE's technology appraisal guidance on cetuximab and panitumumab for previously untreated metastatic colorectal cancer)
- trifluridine–tipiracil alone for mCRC after available therapies (see NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated metastatic colorectal cancer)

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- regorafenib for mCRC after available therapies (see NICE's technology appraisal guidance on regorafenib for previously treated metastatic colorectal cancer)
- 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 anticipated 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 final scope, that is trifluridine–tipiracil, regorafenib and best supportive care. The clinical experts explained that most people would have regorafenib, trifluridine–tipiracil or fruquintinib 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

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to anyone for whom trifluridine–tipiracil 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 meeting, there was an ongoing appraisal that could affect the treatment pathway (see NICE's technology appraisal guidance on trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments). The clinical experts said that there would be a quick uptake of trifluridine–tipiracil with bevacizumab if introduced. The committee concluded that the relevant comparators should be what is used in NHS practice. It considered the current relevant comparators to be regorafenib and trifluridine–tipiracil, but understood that these were likely to change if other treatments were introduced.

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-epidermal growth factor receptor (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),

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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 which 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. Anti-VEGF monotherapy (such as bevacizumab) is not recommended by NICE 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 period 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 stated that none of the participants in FRESCO had previously had treatment with trifluridine–tipiracil or regorafenib, whereas people in FRESCO-2 who were not intolerant had 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 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 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.

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Network meta-analysis

3.6 The company did not have direct clinical-effectiveness evidence for fruquintinib compared with trifluridine–tipiracil 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 difference between fruquintinib and trifluridine–tipiracil (HR 0.95, 95% CI 0.78 to 1.15) or regorafenib (HR 0.93, 95% CI 0.75 to 1.16). Fruquintinib improved progression-free survival compared with trifluridine–tipiracil (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 analysis 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, where 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 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 3.11). 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).

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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 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 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 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 (RECOURSE and Yoshino et al.), which it sourced from the literature. It then fitted independent survival models (generalised gamma) 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

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failure time models used by the company. The committee, in this case, was concerned not with fitting hazard ratios to accelerated time function models but with 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 and, if not, to explore alternative approaches that relax the proportional hazards assumption (such as fractional polynomials or piecewise approaches), before the NMA hazard ratios could be plausibly applied.

Overall survival using SACT data

3.9 In an ongoing mCRC evaluation, the committee requested additional analysis using real-world evidence in the NHS for trifluridine–tipiracil to resolve uncertainty in overall survival modelling (see NICE's technology appraisal guidance on trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments). 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
- using the extrapolated trifluridine–tipiracil curve as the reference curve

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- 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 a small proportion of people having fruquintinib would be alive after 10 years and 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 in 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. The committee concluded that it preferred using the real-world evidence (SACT data) for modelling overall survival for trifluridine–tipiracil because this reflected the expected absolute survival for the relevant population.

Progression-free survival extrapolation

3.10 The company modelled progression-free survival with the same approach used for overall survival (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, 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

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estimate for trifluridine–tipiracil 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 (RECOURSE and Yoshino et al.) 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 progression-free survival trial data, which is generalisable to the NHS, as a reference curve, then 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 further analysis on log-time interaction for each treatment was needed to assess if the proportional hazards assumption held, and, if not, alternative approaches that relax the proportional hazards assumption (such as fractional polynomials or piecewise approaches) should be explored.

Time to treatment discontinuation

3.11 The company 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 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 was not publicly available. The EAG had concerns about the company's approach

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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.) for trifluridine–tipiracil. 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 additional analysis, which assumed only a proportion of people who were progression free would have regorafenib. It estimated this by dividing the mean time on treatment in the regorafenib trial (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 where available and plausible. It concluded that applying a log-normal curve to the digitised trial time to treatment discontinuation data for trifluridine–tipiracil and an exponential curve to the median time on treatment for regorafenib was not ideal but reasonable.

Relative dose intensity

3.12 The company assumed that fruquintinib, regorafenib and trifluridine–tipiracil 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 (89.0%) trials to be consistent with the source of efficacy estimates used in the company's model. The committee asked the clinical experts if these treatments were likely to have the same relative dose intensities. The

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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 NHS England Cancer Drugs Fund (CDF) clinical lead explained that reducing the dose of regorafenib and trifluridine–tipiracil 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.

Subsequent treatment

3.13 The company's base case used pooled FRESCO and FRESCO-2 data to inform the modelling of subsequent treatment. It also assumed 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 would have post-progression treatment. The CDF clinical lead explained that it was unclear if this figure represented all people having treatment across the NHS, including those having treatment within the CDF. The committee recalled the clinical experts' 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-

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progression treatment should be applied with an 8-week treatment duration.

Utility values

3.14 The utility values used in the company's 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 (CORRECT trial; NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated metastatic colorectal cancer, TA405): pre-progression 0.73, post-progression 0.59
- regorafenib (CONCUR and CORRECT trials; NICE's technology appraisal guidance on regorafenib for previously treated metastatic colorectal cancer, TA866): pre-progression 0.72, post-progression 0.59
- bevacizumab with trifluridine-tipiracil (SUNLIGHT trial; NICE's technology appraisal guidance on trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments): 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 recent appraisals (TA866 and TA405) and could lack face validity. It also noted that the utility values were sourced from the FRESCO-2 trial, whereas the clinical-effectiveness data were 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 considered that pooling all the available utility values would have provided useful additional data for decision making, but in the absence of this the

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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.

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 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. It recalled the EAG's perspective about people included in FRESCO being younger than those 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 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 as 1.7. The committee considered that using the SACT data 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, using its preferred source for utility values (see sections 3.8 and 3.14).

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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

Company and EAG cost-effectiveness estimates

3.17 The exact cost-effectiveness estimates cannot be reported here because there are confidential discounts for fruquintinib, regorafenib and trifluridine–tipiracil. Both the company's and EAG's base case incremental cost-effectiveness ratios (ICERs) were above the range that NICE normally considers an acceptable use of NHS resources, even when the QALY weighting was applied. The committee noted that survival extrapolation had a large impact on the cost-effectiveness results and there was uncertainty in both the EAG's and company's approaches to modelling long-term survival. It considered that further analyses are needed to address the uncertainty in the data needed for decision making. The committee requested the following further analyses:

- Considering treatments currently used in NHS clinical practice as comparators, if these change from trifluridine–tipiracil and regorafenib (see section 3.3).
- Exploring the log-time interaction for each treatment to understand the best approach for overall survival extrapolations. If the proportional hazards assumption holds, it would prefer to apply the hazard ratios from the NMA to both the generalised gamma and log-logistic extrapolations of the SACT data for trifluridine–tipiracil and consider the ICERs estimated in both scenarios. If the proportional hazards assumption does not hold, alternative approaches that relax the proportional hazards assumption (such as an NMA with fractional

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polynomials or a piecewise approach) should be explored (see section 3.8).

- Exploring the log-time interaction for each treatment to understand the best approach for extrapolating progression-free survival. If the proportional assumption holds, it would prefer to use trifluridine-tipiracil progression-free survival trial data that is generalisable to the NHS as a reference curve, and to apply the hazard ratios from the NMA to this. If the proportional hazards assumption does not hold, alternative approaches that relax the proportional hazards assumption (such as an NMA with fractional polynomials or a piecewise approach) should be explored (see section 3.10).
- Accurately modelling the acquisition cost of fruquintinib for people having a dose reduction (see section 3.13).
- Applying the pooled estimate of all the relevant utility values in a scenario, and the CORRECT trial utility values for the base case (see section 3.14).
- Updating the QALY shortfall calculation, taking into account the committee's preferred assumptions and its requested analyses on survival modelling and utility values (see section 3.15).

The committee's preferred assumptions were to:

- model time to treatment discontinuation by applying a log-normal curve to the digitised trial data for trifluridine–tipiracil and an exponential curve to the median time on treatment for regorafenib (see section 3.11)
- use trial-specific relative dose intensity for regorafenib and trifluridine–tipiracil (see section 3.12)
- use NHS England estimates of subsequent treatment (35%) and a duration of 8 weeks (see section 3.13)
- use trifluridine-tipiracil SACT data mean age (65 years) to inform the severity weighting estimates (see section 3.15).

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Conclusion

Fruquintinib is not recommended

3.18 The committee took into account its preferred assumptions, the company and EAG base cases, and the key uncertainty related to survival modelling. It concluded that fruquintinib was unlikely to represent a cost-effective use of NHS resources. The committee requested further analyses to inform its decision making. So, it did not recommend fruquintinib for previously treated mCRC.

4 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

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.

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