Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Contents:

The following documents are made available to stakeholders:

1. **Comments on the Draft Guidance from** Takeda UK Ltd

2. **Consultee and commentator comments on the Draft Guidance** from:
   a. Servier Laboratories Ltd

3. **Comments on the Draft Guidance from experts:**
   a. Mark Saunders– clinical expert, nominated by Takeda UK

4. **Comments on the Draft Guidance received through the NICE website**

5. **External Assessment Group critique of company comments on the Draft Guidance**

6. **Company response to committee requests following ACM2**

7. **External Assessment Group critique of company response following ACM2**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Takeda UK Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None.
Name of commentator person completing form:	**********, Market Access Manager – Oncology

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

Executive summary	The Company would like to thank the Evaluation Committee for their consultation on this appraisal. The Company are disappointed with the Committee's provisional draft position not to recommend fruquintinib for patients with previously treated metastatic colorectal cancer (mCRC), and we do not consider this recommendation to be a sound and suitable basis for guidance to the National Health Service (NHS). The Company are keen to collaborate with NICE to ensure a positive recommendation can be made for this indication and hope that the additional information provided in this response will support the NICE Committee to achieve this.
	
	The Company would like to emphasise that there remains an unmet need for later-line treatments with a tolerable and manageable safety profile that do not negatively impact patient quality of life (QoL), and were pleased to see the unmet need recognised by the Evaluation Committee in Section 3.1 of the draft guidance. The Company believe that fruquintinib would serve to address this unmet need by providing an efficacious therapy with minimal off-target toxicity, enabling patients to achieve the maximum clinical benefit of treatment to prolong survival, whilst maintaining good QoL. Preliminary results from a recent Company online patient survey, which included 165 patients in the United Kingdom (UK) with mCRC, further highlights the unmet need felt in the patient community (1):
	• When asked about the factors influencing treatment decisions, the most common answers were impact to physical health (50%), side effects (44%), and QoL implications (42%)
	• In total, 81% of patients noted that they found it discouraging to not have access to all licensed treatment options for mCRC.
	
	As requested in the draft guidance, the Company have provided further analyses and are in agreement with the Committee regarding the majority of preferred assumptions:
	• It is reasonable to use the trifluridine-tipiracil data as the reference curve to estimate comparator efficacy, informed by systemic anti-cancer therapy (SACT) data (Comment 5).
	  ○ It is reasonable to consider an average of the log-logistic and generalised gamma extrapolations of the SACT data.
	• The proportional hazards (PH) assumption is reasonable for overall survival (OS) based on a full assessment, including further analysis as requested by the Committee. Therefore, it is reasonable to apply hazard ratios (HR) from the network meta-analysis (NMA) to the reference curve to estimate OS for fruquintinib, regorafenib, and best supportive care (BSC) (Comment 5).
	• It is reasonable to use the trifluridine-tipiracil data as the reference curve to estimate comparator progression-free survival (PFS), informed by digitised trial data (pooled RECOURSE (2) and Yoshino et al. 2012 (3)) (Comment 5).
	• The PH assumption is also reasonable for PFS, based on a full assessment including further analysis as requested by the Committee; therefore, it is reasonable to apply HRs from the NMA to the reference curve to estimate PFS for fruquintinib, regorafenib, and BSC (Comment 6).
	• The Company have ensured that the acquisition cost of fruquintinib has been accurately modelled (Comment 7).
	• It is reasonable to apply the utility values sourced from the CORRECT trial (absolute; progressed free [PF]:0.73, progressed disease [PD]:0.59) (Comment 8).
	  ○ As requested, the Company have provided a scenario analysis applying a pooled utility value calculated as a weighted average of utility values from the CONCUR, CORRECT, and SUNLIGHT trials (PF: 0.73, PD: 0.64).

- It is reasonable to model trifluridine-tipiracil time-to-treatment discontinuation (TTD) by fitting a log-normal curve to the digitised trial data (pooled RECOURSE (2) and Yoshino et al. 2012 (3)) (Comment 9).
- It is reasonable to model regorafenib TTD by fitting an exponential curve through the median time on treatment reported in the CORRECT trial (7.39 weeks) (Comment 9).
- It is reasonable to model subsequent treatment proportions based on clinical opinion elicited by the Company, use NHS England estimates to inform the proportion of patients receiving active therapy (35%), and assume a duration of 8 weeks (Comment 9).

The Company have therefore presented an updated base case that incorporates the above changes in assumptions to align more closely with the Committee preferred assumptions. In addition, to continue to show flexibility and commitment in this appraisal process, the Company have submitted an enhanced patient access scheme (PAS) proposal to Patient Access Scheme Liaison Unit (PASLU). This is [redacted]. This enhanced net price offer reduces the incremental cost-effectiveness ratio (ICER) to a level which is cost-effective at the £30,000 per quality-adjusted life-year (QALY) threshold, assuming eligibility for the 1.7 severity modifier and a pairwise comparison with regorafenib (Comment 12). This demonstrates the Company's flexibility and commitment to reaching a positive outcome for patients with mCRC.

The Company have provided further discussion around the following Committee preferred assumptions, which the Company do not consider reasonable:

- Potential change in scope to include trifluridine-tipiracil with bevacizumab as a comparator (Comment 2)
- Relative dose intensity (Comment 7)
- Mean age informing severity modifier calculations (Comment 12)

Importantly, the Company would like to reiterate that, as per the position in the original Company submission, regorafenib is considered the most relevant comparator for decision making. As discussed further in Comment 1, this positioning reflects how the majority of fruquintinib use in UK clinical practice is expected to replace current use of regorafenib, as informed by extensive expert clinical feedback obtained via two UK advisory boards (September 2023 and December 2023) and four further one-to-one interviews with UK-based oncologists (October 2024) (4-6).

Based on the revised Company base case and proposed enhanced PAS, fruquintinib is dominant versus regorafenib and is associated with an incremental net health benefit (NHB) of [redacted]. Importantly, fruquintinib remains dominant and NHB remains consistent across scenarios explored in this response to the draft guidance, which were conducted with the aim of addressing uncertainty in the updated Company base case. In relation, the Company would also like to reiterate that it believes NHB is the most appropriate outcome for decision-making given the sensitivity of the ICER due to small incremental QALYs.

In addition, the relevant severity modifier remains 1.7 under the revised Company base case (Comment 12, Appendix A) and all scenarios explored in response to the draft guidance; the Company therefore consider a QALY weighting of 1.7 to be reasonable for decision-making.

	The Company are optimistic that the Committee will reconsider the draft recommendation in light of the additional analyses presented and considerable alignment with the Committee's preferred assumptions, as presented in the revised Company base case. The Company believes that the revised base case provides the most reasonable interpretation of the clinical and cost-effectiveness evidence and that all of the relevant available evidence has been considered.
1	**Treatment pathway** In the draft guidance, the Committee requested "*further analyses considering treatments currently used in NHS clinical practice as comparators, if these change from trifluridine-tipiracil and regorafenib*". Considering treatments currently used in NHS clinical practice, the Company maintain that the relevant comparator for decision-making is regorafenib. As this is not expected to change, the Company consider that further analyses are not required, as discussed further in Comment 2. The Company would like to reiterate that, as per the position in the original Company submission, regorafenib is considered the most relevant comparator for decision-making. The rationale for the expected positioning of fruquintinib is outlined below, which considers the evolving mCRC treatment pathway and is supported by extensive feedback from clinical experts, elicited at two UK advisory boards (September 2023 and December 2023) and four further one-to-one discussions with UK-based oncologists (October 2024) (4-6). The Company agree with the Committee's conclusion that "*fruquintinib would be used as a third-line or later treatment*". The Company also agree that "*there would be a quick uptake of trifluridine–tipiracil with bevacizumab if introduced"*. Given the publication of a positive recommendation for NICE TA1008 in August 2024, trifluridine-tipiracil with bevacizumab is expected to quickly become standard of care for the majority of patients in the third-line setting, in line with the marketing authorisation and in alignment with Committee conclusions in the TA1008 final draft guidance (7). However, the Company believe that trifluridine-tipiracil with bevacizumab is not a relevant comparator for the fruquintinib appraisal, for reasons outlined below. **<u>In patients who are eligible for treatment with trifluridine-tipiracil in combination with bevacizumab</u>** If patients are eligible to receive trifluridine-tipiracil in combination with bevacizumab, clinical experts emphasised how patients would be expected to receive this therapy in the third-line setting over any alternative treatments, including fruquintinib. Therefore, fruquintinib is not expected to replace any use of trifluridine-tipiracil in combination with bevacizumab in the third-line setting. Hence, trifluridine-tipiracil with bevacizumab is not considered a relevant comparator vs fruquintinib. It is expected that following treatment with trifluridine-tipiracil with bevacizumab, patients will currently receive regorafenib in the fourth-line or later setting. As it is expected that fruquintinib will replace current regorafenib use, regorafenib is a relevant comparator vs fruquintinib in the fourth-line and later setting, in those eligible for treatment with trifluridine-tipiracil with bevacizumab at third-line. Furthermore, patients who are eligible for treatment with trifluridine–tipiracil with bevacizumab at third-line are not expected to be eligible to receive re-treatment with trifluridine-tipiracil as a monotherapy in the fourth-line or later setting. Trifluridine-tipiracil monotherapy is therefore not a

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

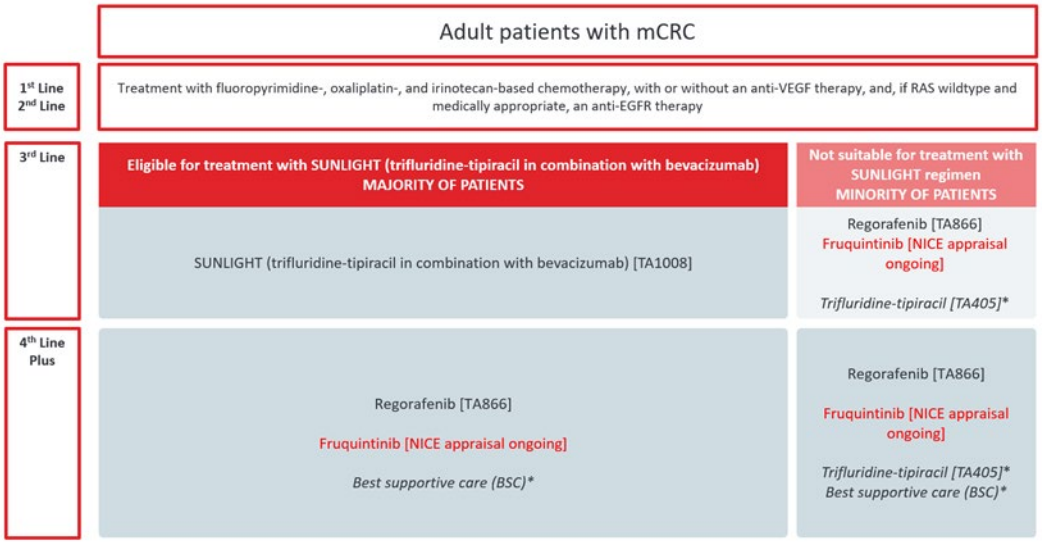
Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	relevant comparator vs fruquintinib at any point of the treatment pathway in patients who are eligible for treatment with trifluridine–tipiracil with bevacizumab at third-line. **<u>In patients who are not eligible for treatment with trifluridine-tipiracil in combination with bevacizumab</u>** While the Company acknowledge that the majority of patients will receive trifluridine-tipiracil with bevacizumab at third-line, a small proportion of patients will not be suitable for this treatment and will instead receive regorafenib. As it is expected that fruquintinib will replace the current use of regorafenib in the third-line setting, regorafenib is considered the most relevant comparator vs fruquintinib. The Company also acknowledge that a very small proportion of patients may receive trifluridine-tipiracil monotherapy (TA405) at third-line if they are not suitable for bevacizumab, or choose to avoid bevacizumab due to the need to visit the hospital for administration. Importantly, while fruquintinib is expected to replace current use of trifluridine-tipiracil monotherapy in this setting, the relevant patient numbers are so small that the Company consider the comparison of trifluridine-tipiracil vs fruquintinib less relevant for decision-making, similarly to how the committee conclude that "*the comparison with best supportive care was less relevant*". In the very small proportion of patients who are not suitable for treatment with trifluridine-tipiracil with bevacizumab and progress on a third-line treatment, it is expected that, depending on prior treatment, they will receive either regorafenib, trifluridine-tipiracil monotherapy or BSC. While it is expected that fruquintinib will predominantly be used in the third-line in this trifluridine-tipiracil with bevacizumab-unsuitable population, the Company acknowledges there may be a very small amount of use of fruquintinib in fourth-line. The comparison with regorafenib, trifluridine-tipiracil monotherapy or BSC in this fourth-line setting is therefore considered less relevant for decision-making. A revised treatment pathway for adult patients with mCRC is presented in Figure 1. This considers the evolving mCRC landscape following the publication of a positive recommendation for NICE TA1008 in August 2024, and has been validated by UK-based oncologists.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	Figure 1: Treatment pathway for adult patients with mCRC  Abbreviations: EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; RAS, rat sarcoma virus; VEGF, vascular endothelial growth factor. Based on this, the Company encourage the NICE committee to consider regorafenib as the most relevant comparator for decision-making, and to provide a recommendation in line with the marketing authorisation of fruquintinib to avoid limiting patient choice given the evolving treatment landscape. Based on the revised Company base case and proposed enhanced PAS, fruquintinib is dominant versus regorafenib and is associated with an incremental NHB of [redacted]. Importantly, fruquintinib remains dominant and NHB remains consistent across scenarios explored in response to the draft guidance, which were conducted with an aim of addressing uncertainty in the updated Company base case.
2	**Potential change in scope to include trifluridine-tipiracil with bevacizumab as a comparator** As per the final scope issued by NICE in December 2023, throughout this appraisal (including in the original Company submission and subsequent external assessment group [EAG] report) regorafenib, trifluridine-tipiracil monotherapy, and BSC have been considered potentially relevant comparators vs fruquintinib. Robust methods have been used to estimate comparative efficacy of fruquintinib vs these comparators throughout the submission including conducting an NMA in line with recommendations in the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 2 and NICE DSU TSD 18 (8, 9). Evidence was presented for fruquintinib vs all three comparators and, as per the original Company submission and rationale presented in Comment 1, of these comparators Takeda consider regorafenib to be the most relevant comparator for decision-making. Throughout this appraisal, the Company have aligned with the NICE methods guide, which states that comparators should reflect "*established clinical practice in the NHS*" and that "*technologies that NICE has recommended with managed access are not considered established practice in the NHS and are not considered suitable comparators*" (10). The Company therefore believe that technologies receiving a separate recommendation from NICE during an ongoing

	appraisal process, especially at this late stage following the first Committee meeting, cannot be considered established practice. The Company therefore do not consider it reasonable for NICE to issue a revised scope at this stage of the appraisal that introduces trifluridine-tipiracil with bevacizumab as a new comparator based on final draft guidance published on 28th August 2024 (TA1008). Given trifluridine-tipiracil with bevacizumab only received a positive recommendation from NICE on 28th August 2024, the Company believe that this treatment could not be considered "*established clinical practice in the NHS"* at the point the revised scope for fruquintinib was released for consultation on 8th October 2024. Furthermore, during the first 90 days following final draft guidance publication, the funding for trifluridine-tipiracil with bevacizumab is provided by the Cancer Drugs Fund (CDF). This is a managed access fund and, as stated above, technologies under managed access are not considered suitable comparators as per the NICE methods guide. The Company believe that the introduction of a new comparator at a late stage in the appraisal process could be perceived as an example of NICE failing to act fairly and consistently across appraisals, whilst having the potential to provide a recommendation which is unreasonable in light of the evidence submitted to NICE. Regardless, as outlined above in Comment 1, Takeda do not believe that trifluridine-tipiracil with bevacizumab is a relevant comparator for decision-making in the appraisal for fruquintinib. Based on clinical expert opinion elicited at two advisory boards and in additional one-to-one discussions, trifluridine-tipiracil with bevacizumab will quickly become standard of care in the third-line setting following the positive recommendation in TA1008 (4-6). Patients who are eligible for treatment with trifluridine-tipiracil with bevacizumab would receive this combination, and not fruquintinib, at third-line. Following this, patients who have received the trifluridine-tipiracil with bevacizumab combination are not expected to be eligible to receive trifluridine-tipiracil monotherapy in the fourth-line and later setting. Instead, patients would receive fruquintinib in the fourth-line setting, replacing regorafenib. Therefore, the Company believe that regorafenib remains the most relevant comparator for decision-making, as in the vast majority of patients, fruquintinib will replace regorafenib use.
3	**NMA results** The draft guidance states that "*for overall survival, there was no difference between fruquintinib and trifluridine-tipiracil or regorafenib*" and that "*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 Company would like to clarify that whilst there was no significant difference, the results of the NMA indicated a numerical improvement in overall survival for fruquintinib versus both trifluridine-tipiracil and regorafenib, and recommends that this is clarified in the draft guidance. To further support this, the Company sought expert clinical input via one-to-one conversations with four UK-based oncologists in October 2024. The clinical experts noted that for this patient population, which is in an advanced stage of disease and undergoing late-line therapy, the most clinically meaningful outcome is delaying progression, provided QoL is maintained. Patients prefer to avoid a prolonged period following progression, as this is associated with worsening of disease-related symptoms and deteriorating QoL. Therefore, when assessing treatments for mCRC, the focus should be on PFS and QoL rather than OS alone. As noted in the Company submission, the NMA results demonstrate that fruquintinib is associated with a statistically significant improvement in PFS compared with all three

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	comparators (regorafenib, trifluridine-tipiracil, and BSC). Although no comparative health-related quality of life (HRQoL) data are available for fruquintinib vs regorafenib or trifluridine-tipiracil, the FRESCO-2 trial demonstrated that HRQoL was not negatively impacted by treatment with fruquintinib (Section B.2.6.2.3 of the Company submission). Moreover, patients in the fruquintinib arm experienced a slower decline in their clinical condition compared with patients in the placebo + BSC arm (as measured using QLQ-C30 and EQ-5D-5L questionnaires). In light of this, and given the statistically significant advantages in PFS and OS for fruquintinib vs placebo + BSC in two Phase III randomised controlled trials (RCTs) (FRESCO and FRESCO-2), and the significant PFS advantage and numerical OS benefit of fruquintinib vs regorafenib and trifluridine-tipiracil in the NMA, we believe this concern should not impact the Committee's decision.
4	**NMA subgroup results** Regarding additional analysis of the impact of potential treatment effect modifiers on NMA results performed by the Company, the draft guidance states that "*The results were broadly similar to the overall NMA results, except for the overall survival of people who had not had anti-vascular endothelial growth factor (VEGF) treatment, where regorafenib showed better overall survival than fruquintinib".* Importantly, with the evolving treatment pathway described in Comment 1, the majority of fruquintinib use in UK clinical practice is expected to be following treatment with trifluridine-tipiracil with bevacizumab, i.e. following an anti-VEGF treatment. The subgroup analysis based on patients who had not received a prior anti-VEGF treatment is therefore considered less relevant than analyses in the patient population who had received a prior anti-VEGF treatment. As presented in Section 2.9.6 of the Company submission, NMA subgroup analyses were conducted based on receipt of prior anti-VEGF treatment. In patients who had received prior anti-VEGF treatment, fruquintinib was associated with a numerical reduction in the risk of death compared with regorafenib (HR: 0.89 [95% credible interval [CrI]: 0.70, 1.15]), which is consistent with the base case NMA results (HR: 0.93 [95% CrI: 0.75, 1.16]) and other subgroup analyses. This analysis was based on a large sample size, with 841/964 patients informing the analysis for regorafenib. Conversely, the analysis in the no prior anti-VEGF treatment population, which is referenced in the EAG report, was based on a very small sample size: the input data for regorafenib were based on only 82/204 of patients from only **one** RCT assessing regorafenib vs BSC (CONCUR). This is a key limitation and is an insufficient sample size to inform a robust analysis. While the Company appreciate that the draft guidance acknowledges 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 Company would like to further emphasise the limitations of this analysis. These limitations, and the fact that the majority of fruquintinib treatment is expected to be following an anti-VEGF treatment in UK clinical practice in light of trifluridine-tipiracil with bevacizumab positive NICE guidance (TA1008), the Company believe the NMA subgroup analyses in patients who have received a prior anti-VEGF therapy are more relevant than the analyses in the patient population who had not received a prior anti-VEGF treatment.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

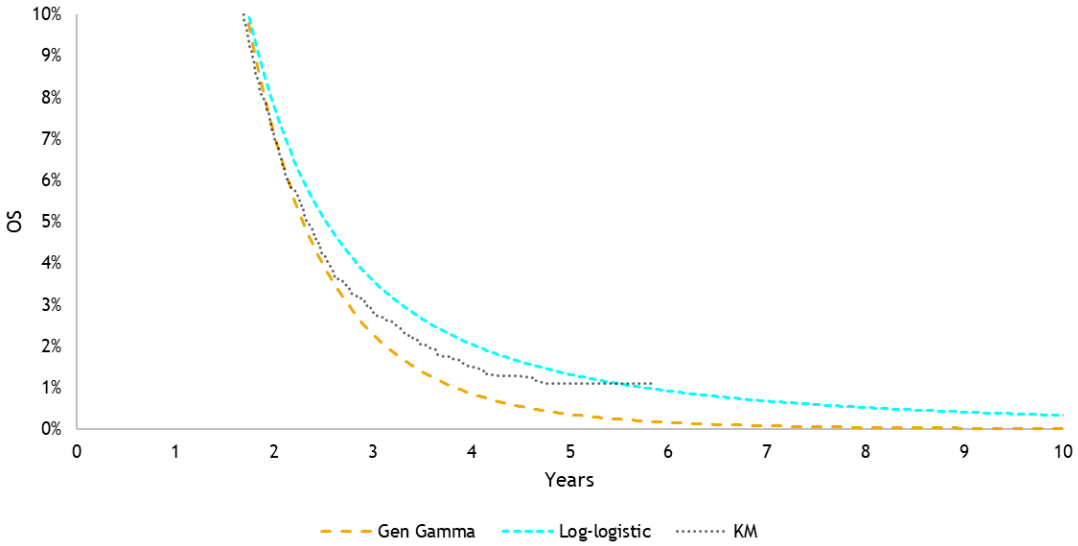
5	**Overall survival extrapolation** The Company agrees with the Committee preferred approach of estimating baseline survival using the trifluridine-tipiracil SACT data and applying NMA HRs to inform comparator efficacy. However, the Company would like to note some limitations with the approach. The draft guidance states that the Committee "*noted its preferred method of survival extrapolation was to apply the NMA hazard ratios for each treatment to real-world evidence"* but requested *"further analysis to assess whether the proportional hazards assumption was appropriate*". The Company have provided further analysis to assess the appropriate OS extrapolation in line with the Committee's request. **<u>The use of SACT data to inform baseline risks for OS</u>** While the Company acknowledge that the SACT data is real world evidence (RWE) collected in a UK population who would be eligible for trifluridine-tipiracil (adults with mCRC whose disease has progressed after standard therapies or for whom standard therapies are unsuitable as per TA405), and that clinical outcomes align with published literature (Table 4), the Company believe that there are limitations associated with using the SACT OS data to inform the model base case: • Many key data that are required to assess the appropriateness of the SACT data were not made available to the Company. Importantly, there are no data available on the baseline characteristics of the patient population which these data are based on. Without these data, the Company is unable to verify whether the population informing the SACT data is consistent with the populations of the respective trials that are used to inform comparative efficacy for fruquintinib, regorafenib, trifluridine-tipiracil, and BSC via the NMA. • In relation, as there are no detail available on baseline characteristics beyond mean age, the Company is unable to verify whether the population aligns with the population expected to receive fruquintinib in clinical practice within the UK. • No PFS, adverse event (AE), subsequent treatment, or TTD data were available from the SACT dataset. Therefore, the Committee's preferred base case includes a mix of data sources (i.e. from a mix of clinical trial and real-world data), and therefore a mix of patient populations to inform clinical data in the model. As only OS data are available from SACT, it is not possible to have consistent data sources for OS, PFS, and TTD in the model. Despite limitations with the SACT data, the Company acknowledge the similarity in OS outcomes between SACT and key RCTs assessing trifluridine-tipiracil (2, 3). The SACT data have therefore been used to inform OS for trifluridine-tipiracil in the revised Company base case. The draft guidance states that "*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 EAG preferred a generalised gamma distribution; however, the Company is cognisant that this distribution does not predict outcomes that align with clinical expert opinion which highlighted that a small percentage of patients may still be alive at 10 years. Therefore, the Company agree that an average of the generalised gamma and log-logistic distributions, as requested by the Committee, is more appropriate. Both distributions are presented in Figure 2. This approach was also accepted by the Committee for decision-making in the trifluridine-tipiracil with bevacizumab appraisal (7).

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 2: Generalised gamma and log-logistic distribution, SACT OS



Abbreviations: KM, Kaplan Meier; OS, overall survival; SACT, systemic anti-cancer therapy.

The Company agree with the Committee that it is preferable to apply NMA HRs to the SACT data to inform comparator OS vs the EAG preferred approach, which "*would not preserve randomisation*". As the Committee's preferred approach for modelling OS is to use trifluridine-tipiracil as the reference curve informed by SACT data, the Company consider that the most appropriate assessment of PH should be based on the SACT data for trifluridine-tipiracil vs other comparators (fruquintinib, regorafenib, BSC). The appropriateness of the PH assumption was assessed as per the NICE DSU TSD 14 (11).

Trifluridine-tipiracil (SACT) vs fruquintinib (pooled FRESCO and FRESCO-2 data)

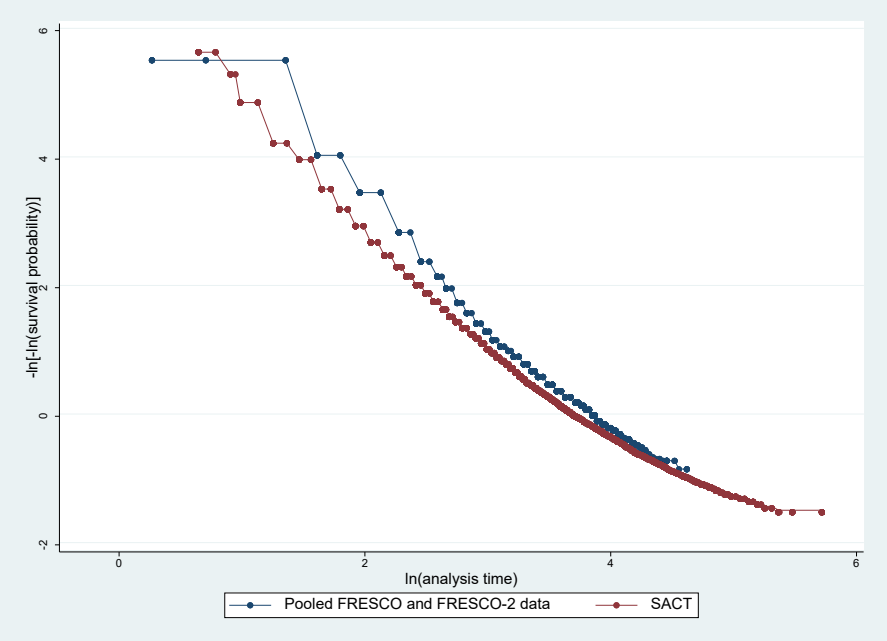
The assessment of the log-cumulative hazard plots for OS suggested no violation of the PH assumption, as the plots are relatively parallel over time (Figure 3).

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 3: Log-cumulative hazard plots, SACT vs pooled FRESCO and FRESCO-2 data, OS



Abbreviations: OS, overall survival; SACT, systemic anti-cancer therapy.

In addition, the global test of the PH assumption provided a p-value greater than 0.05 (p=0.1476), and so the null hypothesis of PH was not rejected at the 95% level of confidence, which further supports PH holding.

In the draft guidance consultation, the Committee requested tests of the interaction between treatment group and time. These tests aim to assess whether there is a change in the treatment effect over time, and therefore whether the assumption of PH is reasonable. However, it should be noted that these tests are not recommended in NICE DSU TSD 14 (11) and are subject to limitations that mean results should be interpreted with caution. For example, including too many interactions terms risks overfitting to the data, where the model captures random noise rather than the underlying relationships within the data. Additionally, studies are typically under-powered for this type of assessment, and the test may be inappropriate if its functional form is not specified correctly. The Company therefore consider other approaches that are recommended in NICE DSU TSD 14, such as the log-cumulative hazard and global test of PH presented, to be more reliable means to assess the PH assumption.

Nonetheless, in response to the Committee's request, tests of the interaction between treatment group and time have been conducted between the SACT data and the pooled FRESCO and FRESCO-2 data. The interaction between time and treatment group, as well as between log-time and treatment group, was significant for both OS and PFS ($p<0.05$) suggesting that the association between treatment effect and outcomes is not independent of time (Table 1). The associated plot is presented in Figure 4. The Company appreciate that the plot and interaction tests suggest that the PH assumption may not hold. However, the Company reiterate that other approaches are more suitable for assessing the PH assumption and, when considered together, the Company believe the PH assumption is reasonable.

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 1: Time and treatment group interaction tests, SACT vs pooled FRESCO and FRESCO-2 data, OS

	HR (CI)	p-value
Interaction with time	1.007 (1.002, 1.013)	0.009
Interaction with log-time	1.249 (1.082, 1.441)	0.002

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 4: Time and treatment group interaction, SACT vs pooled FRESCO and FRESCO-2 data, OS

Abbreviations: HR, hazard ratio; OS, overall survival; PH, proportional hazards; vs, versus.

As discussed in the original Company submission, experts at the UK market access advisory board (1st December 2023) stated that, as OS is short in mCRC population relevant to this appraisal, it was reasonable to assume that the PH assumption would hold between treatments (5). In particular, clinical experts agreed that PH would be expected to hold between fruquintinib, regorafenib and trifluridine-tipiracil, as none of these treatments are considered to change the natural course of disease over time.

In addition, in the regorafenib and trifluridine-tipiracil with bevacizumab NICE appraisals (TA866 and TA1008), it was agreed that the PH assumption held between all treatments, including between regorafenib and trifluridine-tipiracil, based on a similar assessment of diagnostic plots (7, 12). As fruquintinib and regorafenib have similar mechanisms of action, both targeting vascular endothelial growth factor receptors (VEGFR), it is considered reasonable that this assumption would also apply between fruquintinib and trifluridine-tipiracil.

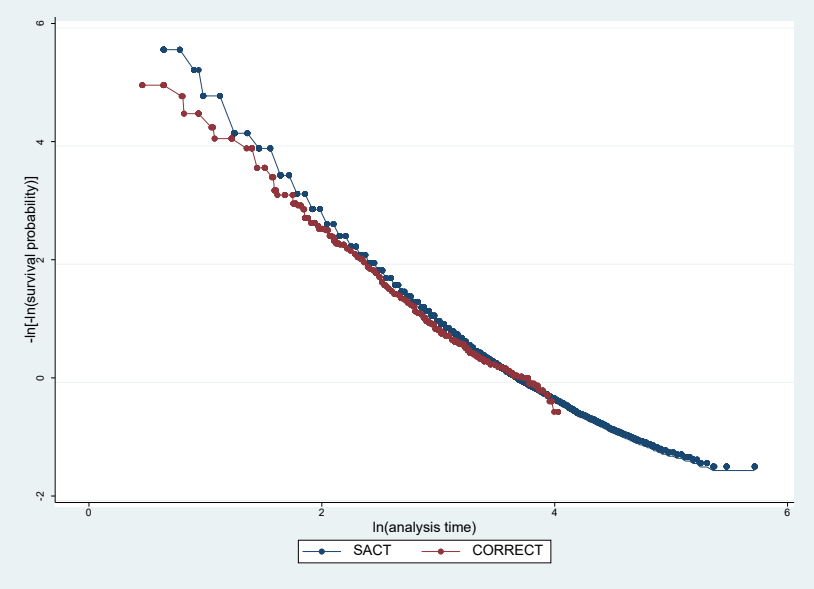
The Company therefore conclude that the PH assumption holds for OS between trifluridine-tipiracil and fruquintinib based on the supporting evidence from the log-cumulative hazard plots, global test of the PH assumption, clinical and health economic expert opinion, and precedence in prior NICE TAs.

Trifluridine-tipiracil (SACT) vs regorafenib (CORRECT)

The assessment of the log-cumulative hazard plots for OS suggested no violation of the PH assumption. Although the plots do converge towards the end of the follow-up period (when the

number of patients at risk is reduced), the plots are comparable for the majority of the time period and are relatively parallel over time (Figure 5).

Figure 5: Log-cumulative hazard plots, SACT vs CORRECT data, OS



Abbreviations: OS, overall survival; SACT, systemic anti-cancer therapy.

In addition, the global test of the PH assumption provided a p-value greater than 0.05 (p=0.4571), and so the null hypothesis of PH was not rejected at the 95% level of confidence, which further supports PH holding.

As previously discussed, the Company consider there to be the limitations in the tests of the interaction between treatment group and time requested by the Committee, and consider other approaches that are recommended in NICE DSU TSD 14 such as the log-cumulative hazards and global test of PH presented, to be a more robust assessment of the PH assumption.

Regardless, in response to the Committee's request, tests of the interaction between treatment group and time have been conducted between the SACT data and CORRECT data. The interaction between time and treatment group, and between log-time and treatment group, was significant for OS ($p<0.05$), suggesting that the association between treatment effect and outcomes is not independent of time (Table 2). The associated plot is presented in Figure 6. The Company appreciate that the plot and interaction tests suggest that the PH may not hold, however reiterate that other approaches are more suitable for assessing the PH assumption.

Table 2: Time and treatment group interaction tests, SACT vs CORRECT data, OS

	HR (CI)	p-value
Interaction with time	0.987 (0.975, 0.999)	0.036
Interaction with log-time	0.806 (0.675, 0.962)	0.017

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; SACT, systemic anti-cancer therapy.

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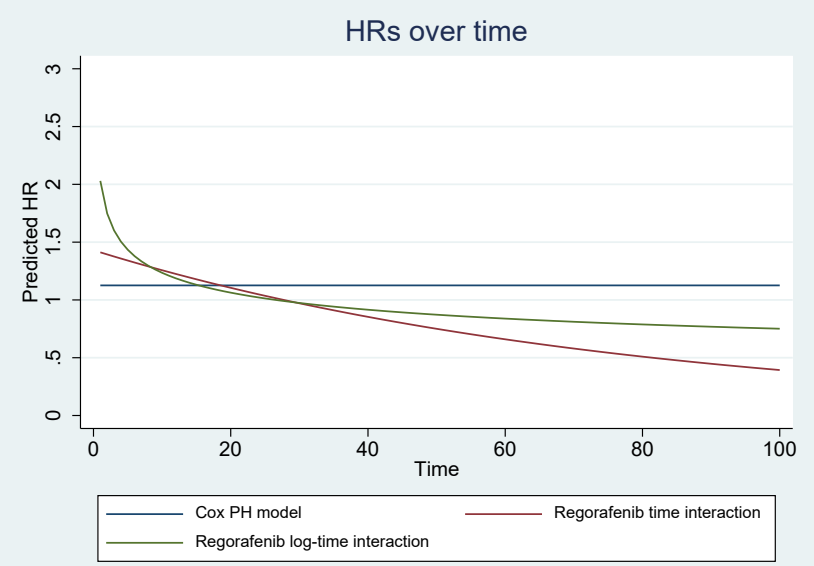
Figure 6: Time and treatment group interaction, SACT vs CORRECT data, OS



Abbreviations: HR, hazard ratio; OS, overall survival; PH, proportional hazards; vs, versus.

As discussed in the original Company submission, experts at the UK market access advisory board (1st December 2023) stated that as the OS is short in the mCRC population relevant to this appraisal, it was reasonable to assume that the PH assumption would hold between treatments (5). In particular, clinical experts agreed that PH would be expected to hold between fruquintinib, regorafenib and trifluridine-tipiracil, as none of these treatments are considered to change the natural course of disease over time.

In addition, in the regorafenib NICE appraisal (TA866), it was agreed that the PH assumption held between all treatments, including between regorafenib and trifluridine-tipiracil, based on a similar assessment of diagnostic plots (12). This was also considered a reasonable assumption in NICE TA1008, where the Committee stated that "*the proportional hazards assumption was likely to hold for OS*" (7).

The Company therefore conclude that, although there is uncertainty regarding the time and treatment group interaction tests, it's reasonable to assume the PH assumption holds for OS between trifluridine-tipiracil and regorafenib based on the supporting evidence from the log-cumulative hazard plots, global test of the PH assumption, clinical and health economic expert opinion, and precedence in prior NICE TAs.

It should also be noted that in both TA866 (12) and TA405 (13), the Committee concluded that the PH assumption held between regorafenib and BSC, and trifluridine-tipiracil and BSC, respectively.

Therefore, the Company conclude that the PH assumption holds between all active therapies for OS. A summary of the PH assumption across treatments is presented in Table 3 for OS.

Table 3: PH assumption summary, OS

	Regorafenib	Trifluridine-tipiracil
Fruquintinib	PH holds	PH holds
BSC	PH holds	PH holds
Regorafenib	–	PH holds

Abbreviations: BSC, best supportive care; OS, overall survival; PH, proportional hazards.

The Company therefore consider that it is reasonable to apply HRs from the NMA to a reference curve to inform efficacy, and do not consider it needed to explore more complex models such as fractional polynomials or splines, as suggested by the Committee in the draft guidance. Specifically, more complex methods are recommended by TSD 14 (Figure 3) when residual plots (e.g. log-cumulative hazard plots) are not straight lines, to enable extrapolations to fit to more complex hazard functions. Given the lines in the log-cumulative hazard plots are relatively straight across assessments, the Company does not believe more complex methods would be informative for decision-making. Furthermore, as the standard parametric approaches recommended in TSD 14 were considered a good fit to the data (Company submission, Section B.3.3.2.1), the estimation of more flexible survival models is not considered necessary, and may induce greater uncertainty in the analysis.

Applying NMA HRs to SACT data to estimate fruquintinib, regorafenib, and BSC OS

The Company agree with the Committee that it is preferable to apply NMA hazard ratios to a reference curve to inform comparator overall survival versus the EAG preferred approach. This approach is supported by the assessments of PH presented, which demonstrate that it is reasonable to assume that the PH assumption holds for trifluridine-tipiracil vs fruquintinib, regorafenib and BSC for OS.

In addition, the same approach was accepted for decision making by the Committee in the recently published NICE TA1008, which assessed trifluridine-tipiracil in combination with bevacizumab vs trifluridine-tipiracil, regorafenib, and BSC (7). In reference to the approach to modelling OS between treatments, the Committee stated that "*a hazard ratio assuming proportional hazards could reasonably be applied*". The Company therefore consider it reasonable to adopt a similar approach in this appraisal.

Regardless, the Company would like to emphasise that this approach may underestimate the OS benefit of fruquintinib. A comparison of modelled outcomes vs observed clinical trial data and RWE is presented in Table 4. It is well documented in the literature that outcomes in RWE are generally worse than outcomes in trial settings (14), and therefore the absolute benefit of fruquintinib will be underestimated when using RWE to inform baseline risks, compared with the trial data. The median OS predicted by the Committee's preferred approach for regorafenib ([redacted] months), trifluridine-tipiracil ([redacted] months) and BSC ([redacted] months) is aligned with the literature which reports median OS in the ranges of 5.6–8.8 months (12, 15-19), 5.8–9.0 months (2, 3, 7, 13, 20-22) and 4.8–7.1 months (2, 3, 12, 13, 15-19, 21, 23-26), for regorafenib, trifluridine-tipiracil, and BSC, respectively. However, the modelled median OS for fruquintinib (7.4 months) is lower than the observed data from the pooled FRESCO and FRESCO-2 trials (8.0 months) (26) and Xu et al. (7.7 months) (25).

Therefore, while the Company have adopted this approach in the revised Company base case, the Committee's preferred approach may underestimate both absolute survival and hence the potential absolute survival benefit associated with fruquintinib in patients with 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. Fruquintinib remains dominant vs regorafenib with the updated base case assumptions and is associated with an incremental NHB of [redacted]

To explore this further, a scenario analysis is presented using an independent modelling approach for the fruquintinib arm and extrapolating the Kaplan Meier (KM) from the pooled FRESCO and FRESCO-2 data using a generalised gamma distribution, which also relaxes the PH assumption between trifluridine-tipiracil and fruquintinib. The most reasonable survival curves for each endpoint were selected as per the approach detailed in Section B.3.3.2 of the Company submission, in line with the recommended approach outlined in NICE DSU TSD 14. This approach more accurately reflects the absolute OS benefit of fruquintinib (median: [redacted] months) compared with the Committee's preferred assumption. This scenario had a minimal impact on cost-effectiveness results in the model, with fruquintinib remaining dominant vs regorafenib and increasing the incremental NHB of fruquintinib vs regorafenib from [redacted] to [redacted].

Table 4: Comparison of OS outcomes

Approach	Median OS, months
Fruquintinib	
Original Company base case (extrapolation of pooled FRESCO and FRESCO data)	8.0
Committee preferred assumptions (NMA HR applied to SACT OS curve (weighted generalised gamma and log-logistic)	7.4
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	7.8
FRESCO (23)	9.3
FRESCO-2 (24)	7.4
Xu, 2012 (25)	7.7
Pooled FRESCO and FRESCO data (26)	8.0
Regorafenib	
Original Company base case (NMA HR applied to fruquintinib OS curve)	7.6
Committee preferred assumptions (NMA HR applied to SACT OS curve)	6.9
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	6.9
CORRECT (16)	6.4
CONCUR (17)	8.8
TA866 model predicted value (12)	7.1
Pooled CORRECT and CONCUR (12, 16, 17)	6.9
REBECCA RWE study (18)	5.6
CORRELATE RWE study (19)	7.7
RECORA RWE study (15)	5.8
Trifluridine-tipiracil	
Original Company base case (NMA HR applied to fruquintinib OS curve)	7.6
Committee preferred assumptions (digitised SACT OS curve)	7.1
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	7.1

RECOURSE (2)	7.2
TERRA (21)	7.8
Yoshino (3)	9.0
TA405 model predicted value (13)	7.4
Pooled RECOURSE and Yoshino (13)	7.3
Trifluridine-tipiracil monotherapy reported in SUNLIGHT (7)	7.5
Tong 2021 RWE study (22)	5.8
Stavraka 2021 RWE study (20)	7.6
BSC	
Original Company base case (extrapolation of pooled FRESCO and FRESCO data)	5.3
Committee preferred assumptions (NMA HR applied to SACT OS curve)	5.5
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	5.5
FRESCO (23)	6.6
FRESCO-2 (24)	4.8
Xu, 2012 (25)	5.5
Pooled FRESCO and FRESCO data (26)	5.5
CORRECT (16)	5.0
CONCUR (17)	6.3
Pooled CORRECT and CONCUR (12, 16, 17)	5.3
TA405 model predicted value (13)	5.3
RECOURSE (2)	5.2
TERRA (21)	7.1
Yoshino (3)	6.6
Pooled RECOURSE and Yoshino (13)	5.4

Abbreviations: BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RWE, real world evidence; SACT, systemic anti-cancer therapy

Summary

In summary, the updated Company base case is aligned with the Committee's preferred assumptions of:

- Applying a parametric model (an average of the generalised gamma and log-logistic) to SACT data for trifluridine-tipiracil
- Using the extrapolated trifluridine-tipiracil curve as the reference curve
- Applying the NMA hazard ratios for fruquintinib, regorafenib and BSC to the reference curve to derive OS estimates
    - After a full assessment of the PH assumption, including further testing requested by the Committee, the Company believe that, on balance, the PH assumption is reasonable between fruquintinib, regorafenib and trifluridine-tipiracil

Table 5 presents a summary of the submitted Company base case, the EAG base case, the Committee's preferred assumptions, and the updated Company base case for the estimation of OS for model comparators. The updated base case results and scenario analyses are presented in Appendix A. Fruquintinib remains dominant vs regorafenib with the updated base case

assumptions and additional scenario analysis using independent extrapolations of pooled FRESCO and FRESCO-2 data and is associated with an incremental NHB of [redacted].

Table 5: OS estimation methods

Treatment	Submitted Company base case	EAG base case	Committee's preferred assumptions	Updated Company base case
Fruquintinib	Joint parametric survival model based on pooled FRESCO and FRESCO-2 data	Independent survival model based on pooled FRESCO and FRESCO-2 data	NMA HRs applied to the trifluridine-tipiracil OS curve	NMA HRs applied to the trifluridine-tipiracil OS curve
BSC	Joint parametric survival model based on pooled FRESCO and FRESCO-2 data	Independent survival model based on pooled FRESCO and FRESCO-2 data	NMA HRs applied to the trifluridine-tipiracil OS curve	NMA HRs applied to the trifluridine-tipiracil OS curve
Regorafenib	NMA HR applied to fruquintinib OS curve	Independent curves fit to digitised KM data from the CORRECT study	NMA HRs applied to the trifluridine-tipiracil OS curve	NMA HRs applied to the trifluridine-tipiracil OS curve
Trifluridine-tipiracil	NMA HR applied to fruquintinib OS curve	Independent curves fit to digitised KM data from the pooled RECOURSE and Yoshino studies	Independent curve fit to digitised KM data from SACT	Independent curve fit to digitised KM data from SACT

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; KM, Kaplan Meier; NMA, network meta-analysis; OS, overall survival; SACT, systemic anti-cancer therapy

6

Progression-free survival extrapolation

The company agrees with the Committee preferred approach of estimating baseline survival using the trifluridine-tipiracil pooled RECOURSE/Yoshino data and applying NMA HRs to inform comparator efficacy. However, the Company would like to note some limitations with the approach.

The draft guidance states that 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*". The Company have provided further analysis to assess the appropriate PFS extrapolation in line with the Committee's request.

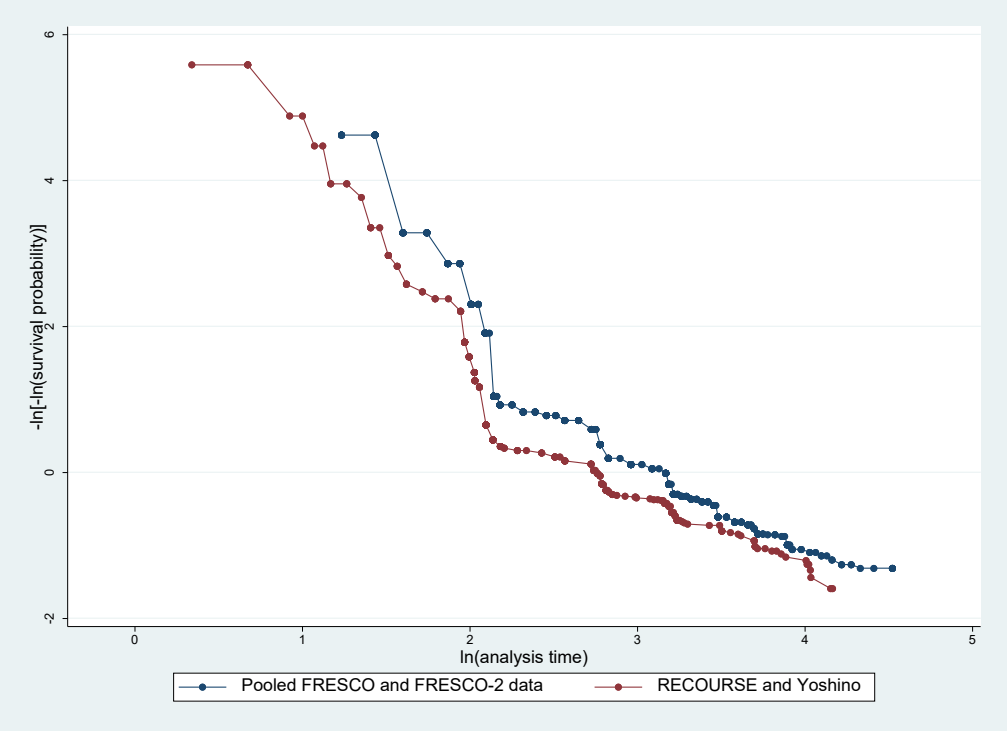
<u>The use of digitised RECOURSE and Yoshino data to inform baseline risks for PFS</u>

The Company acknowledge that in the absence of SACT data for PFS, the digitised RECOURSE and Yoshino data may be considered the most reasonable source of data to inform baseline risks for PFS. However, the Company consider that there are limitations with using the pooled RECOURSE and Yoshino studies to inform the model base case:

- Although PFS KM data are available from a pooled dataset that includes the RECOURSE and Yoshino et al trials, this does not represent the complete evidence base. TERRA is another key Phase III RCT assessing trifluridine-tipiracil vs BSC and was used to inform the comparative evidence base in TA866. TERRA was also identified in the systematic

	literature review (SLR) and considered a relevant trial to inform a robust network to inform comparative efficacy estimates based on a feasibility assessment. The TERRA trial data were not available for analysis at the time of Company submission in TA405, but was raised as a relevant ongoing study expected to mirror the RECOURSE study. The pooled data including all relevant trials (RECOURSE, Yoshino, and TERRA) is therefore considered to be the most reasonable source for trifluridine-tipiracil clinical inputs given that this incorporates all of the available evidence and hence reduces uncertainty in analyses. As there are no publicly available pooled KM data for RECOURSE, Yoshino, and TERRA, the Committee's preferred base case does not reflect the most complete source of trifluridine-tipiracil data. • As there are no SACT data available for PFS, the Committee's preferred approach also results in mixed data sources for OS, PFS, and TTD in the model. As highlighted in Comment 1, outcomes in RWE are generally worse than in trial data, so these data mismatches may induce bias in the analysis. While the Company want to acknowledge these limitations, these data have ultimately been used to inform trifluridine-tipiracil efficacy in the revised Company base case in alignment with the Committee's preferred assumptions. As with OS, and as discussed in the response to Comment 1, the Company agrees with the Committee that it is preferable to apply NMA hazard ratios to a reference curve to inform comparator PFS. The Committee's preferred approach for PFS is to use trifluridine-tipiracil as the reference curve, informed by trifluridine-tipiracil pooled trial (RECOURSE and Yoshino) data (13). Therefore, for PFS, the reasonable assessment of PH is between pooled RECOURSE and Yoshino data and other comparators (fruquintinib, regorafenib, BSC). The appropriateness of the PH assumption was assessed as per NICE DSU TSD 14 (11), several tests were conducted to assess the appropriateness of the PH assumption. **<u>Trifluridine-tipiracil (pooled RECOURSE and Yoshino) vs fruquintinib (pooled FRESCO and FRESCO-2 data)</u>** The assessment of the log-cumulative hazard plots for PFS indicate no violation of the PH assumption, as the plots are clearly parallel over time (Figure 7).

Figure 7: Log-log plots, RECOURSE and Yoshino vs pooled FRESCO and FRESCO-2 data, PFS



Abbreviations: PFS, progression-free survival; SACT, systemic anti-cancer therapy.

The global test of the PH assumption provided a p-value less than 0.05 (p=0.0151), meaning that the null hypothesis of PH is rejected at the 95% level of confidence, which indicates that the PH assumption may not be valid.

As previously discussed, the Company consider there to be the limitations in the tests of the interaction between treatment group and time requested by the Committee, and consider other approaches that are recommended in NICE DSU TSD 14 such as the log-cumulative hazards and global test of PH presented, to be a more robust assessment of the PH assumption.

Regardless, as per the Committee's request, tests of the interaction between treatment group and time between the pooled RECOURSE and Yoshino data and the pooled FRESCO and FRESCO-2 data were performed. The interaction between time and treatment group, as well as between log-time and treatment group, was significant for both OS and PFS (p<0.05) suggesting that the association between treatment effect and outcomes is not independent of time (Table 6). The associated plot is presented in Figure 8. The Company appreciate that the plot and interaction tests suggest that the PH may not hold, however reiterate that there are significant uncertainties with regards to the use of time and treatment group interaction tests to determine if the PH assumption is appropriate and that other approaches may be more suitable for assessing the PH assumption, as discussed in the response to Comment 5.

Table 6: Time and treatment group interaction tests, RECOUSE/Yoshino vs pooled FRESCO and FRESCO-2 data, PFS

	HR (CI)	p-value
Interaction with time	1.019 (1.004, 1.019)	0.011
Interaction with log-time	1.518 (1.188, 1.941)	0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 8: Time and treatment group interaction, RECOUSE/Yoshino vs pooled FRESCO and FRESCO-2 data, PFS

Abbreviations: HR, hazard ratio; PFS, progression-free survival; PH, proportional hazards; vs, versus.

At the UK market access advisory board (1st December 2023), clinical experts agreed that PH would be expected to hold between active therapies, as treatments are not changing the course of disease in this population, only delaying progression.

In the regorafenib and trifluridine-tipiracil with bevacizumab NICE appraisals (TA866 and TA1008), it was agreed that the PH assumption held between all treatments, including between regorafenib and trifluridine-tipiracil, based on a similar assessment of diagnostic plots (7, 12). As fruquintinib and regorafenib have similar mechanisms of action, both targeting VEGFR, it is considered reasonable that this assumption would also apply between fruquintinib and trifluridine-tipiracil.

The Company acknowledge that there is some uncertainty but, on balance, conclude that it is reasonable to assume the PH assumption holds for PFS between trifluridine-tipiracil and fruquintinib based on the supporting evidence from the log-cumulative hazard plots, clinical and health economic expert opinion, and precedence in prior NICE TAs.

Trifluridine-tipiracil (RECOURSE and Yoshino) vs regorafenib (CORRECT)

The assessment of the log-cumulative hazard plots for PFS suggest no violation of the PH assumption (Figure 9); whilst the curves appear to converge with time, this is likely due to low numbers of patients at risk towards the end of the analysis time. The initial shapes of the curves are parallel until approximately (ln(time) = 2), 8.3 months, at which point fewer than 12 (5%) patients remain at risk in the CORRECT trial (16).

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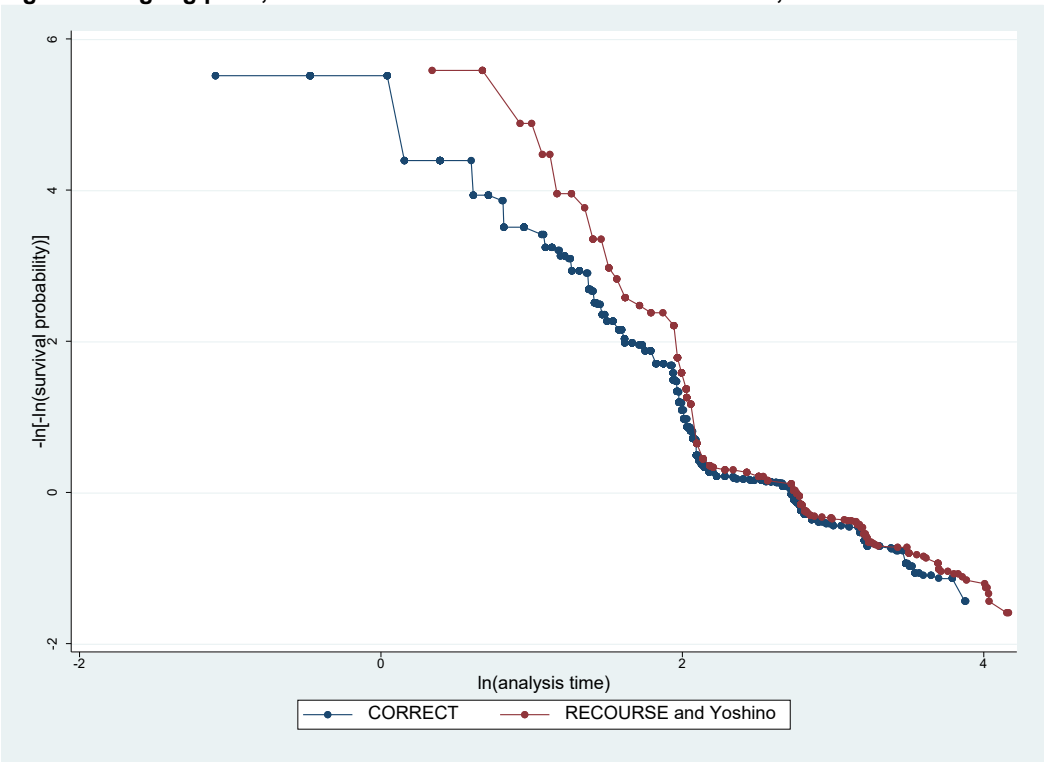
Figure 9: Log-log plots, RECOURSE and Yoshino vs CORRECT data, PFS



Abbreviations: PFS, progression-free survival.

The global test of the PH assumption provided a p-value greater than 0.05 (p=0.7644), meaning that the null hypothesis of PH could not be rejected at the 95% level of confidence, which further supports PH holding.

As previously discussed, the Company consider there to be the limitations in the tests of the interaction between treatment group and time requested by the Committee, and consider other approaches that are recommended in NICE DSU TSD 14 such as the log-cumulative hazards and global test of PH presented, to be a more robust assessment of the PH assumption.

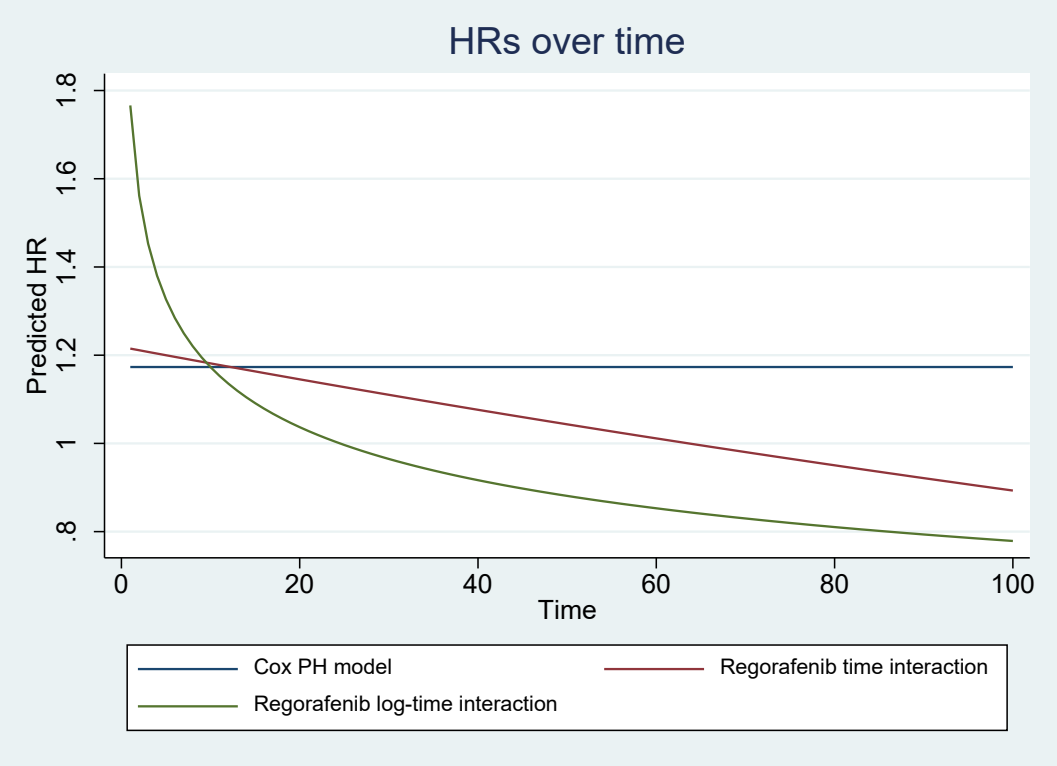
Regardless, as per the Committee's request, tests of the interaction between treatment group and time were performed. The interaction between time and treatment group, as well as between log-time and treatment group, was not statistically significant for both OS and PFS (p>0.05) suggesting that the null hypothesis is not rejected, and that the PH assumption may be reasonable (Table 7). The associated plot is presented in Figure 10.

Table 7: Time and treatment group interaction tests, RECOURSE and Yoshino vs CORRECT, PFS

	HR (CI)	p-value
Interaction with time	0.997 (0.979, 1.016)	0.743
Interaction with log-time	0.837 (0.656, 1.068)	0.153

Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Figure 10: Time and treatment group interaction, RECOURSE and Yoshino vs CORRECT data, PFS



Abbreviations: HR, hazard ratio; PFS, progression-free survival; PH, proportional hazards; vs, versus.

As discussed in the original Company submission, experts at the UK market access advisory board (1st December 2023) stated that as the OS is short in the mCRC population relevant to this appraisal, it was reasonable to assume that the PH assumption would hold between treatments for PFS (5). In particular, clinical experts agreed that PH would be expected to hold between fruquintinib, regorafenib and trifluridine-tipiracil, as none of these treatments are considered to change the natural course of disease over time, only delaying progression.

In the regorafenib NICE appraisal (TA866), it was agreed that the PH assumption held between all treatments, including between regorafenib and trifluridine-tipiracil, based on a similar assessment of diagnostic plots (12). It should also be noted that in both TA866 and TA405, the Committee concluded that PH held between regorafenib and BSC, and trifluridine-tipiracil and BSC, respectively (12, 13), therefore it is reasonable to assume that PH would hold between regorafenib and trifluridine-tipiracil. This was also considered a reasonable assumption in NICE TA1008, where the Committee stated that "*the proportional hazards assumption was likely to hold for OS and PFS*".

The Company conclude that the PH assumption holds for PFS between trifluridine-tipiracil and regorafenib based on the supporting evidence from the log-cumulative hazard plots, Global test of PH, log-time interaction tests, clinical and health economic expert opinion, and precedence in prior NICE TAs.

A summary of the PH assumption across treatments is presented in Table 8 for PFS.

Table 8: PH assumption summary, PFS

	Regorafenib	Trifluridine-tipiracil
Fruquintinib	PH holds	PH holds
BSC	PH holds	PH holds
Regorafenib	–	PH holds

Abbreviations: BSC, best supportive care; PFS, progression-free survival; PH, proportional hazards.

The Company therefore consider that it is reasonable to apply HRs to a reference curve to inform comparator PFS, and therefore do not consider it appropriate to explore more complex models such as fractional polynomials or splines, as suggested by the Committee in the draft guidance. As the standard parametric approaches recommended in TSD14 were considered a good fit to the data (Company submission, Section B.3.3.2.1), the estimation of more flexible survival models was not considered necessary, and may induce greater uncertainty in the analysis.

Applying NMA HRs to digitised RECOURSE and Yoshino data to estimate fruquintinib, regorafenib, and BSC PFS

The Company agrees with the Committee that it is preferable to apply NMA hazard ratios to a reference curve to inform comparator PFS versus the EAG preferred approach. This approach is supported by the assessments of PH presented, which demonstrate that it is reasonable to assume that the PH assumption holds for trifluridine-tipiracil versus fruquintinib, regorafenib and BSC for PFS.

In addition, this approach was accepted for decision making by the Committee in the recently published NICE TA1008, which assessed trifluridine-tipiracil in combination with bevacizumab vs trifluridine-tipiracil, regorafenib, and BSC (7), in which PH was considered to hold in this appraisal between regorafenib and trifluridine-tipiracil based on a similar evidence base. The Company therefore consider it reasonable to adopt a similar approach in this appraisal.

Regardless, the Company would like to emphasise that this approach may underestimate the PFS benefit of fruquintinib. A comparison of modelled outcomes vs observed clinical trial data and RWE is presented in Table 9. The predicted median PFS for regorafenib ([redacted] months), trifluridine-tipiracil ([redacted] months), and BSC ([redacted] months) is aligned with the range of median PFS reported in the literature for all, 1.9–3.2 months, 1.9–3.2 months and 1.0–1.8 months, respectively. However, the predicted median PFS ([redacted] months) for fruquintinib was lower that the range of observed median PFS data reported in for key RCTs (3.7–4.7 months, Table 9). Therefore, the Committee's preferred approach underestimates both absolute PFS and the absolute PFS benefit associated with fruquintinib.

To explore this further, a scenario analysis is presented using an independent modelling approach for the fruquintinib arm and extrapolating the KM from the pooled FRESCO and FRESCO-2 data using a log-normal distribution, which also relaxes the PH assumption between trifluridine-tipiracil and fruquintinib. The most appropriate survival curve was selected as per the approach detailed in Section B.3.3.2 of the Company submission, in line with the recommended approach outlined in NICE DSU TSD 14. This approach more accurately reflects the PFS benefit of fruquintinib (median: [redacted] months) compared with the Committee's preferred assumption. This scenario had a minimal impact on cost-effectiveness results in the model, with fruquintinib remaining dominant vs regorafenib and increasing the incremental NHB of fruquintinib vs regorafenib from [redacted] to [redacted].

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

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Table 9: Comparison of PFS outcomes

Approach	Median PFS, months
Fruquintinib	
Original Company base case (extrapolation of pooled FRESCO and FRESCO data)	3.7
Committee preferred assumptions (NMA HR applied to digitised RECOURSE and Yoshino PFS curve)	3.5
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	3.7
FRESCO (23)	3.7
FRESCO-2 (24)	3.7
Xu, 2012 (25)	4.7
Pooled FRESCO and FRESCO data (26)	3.7
Regorafenib	
Original Company base case (NMA HR applied to fruquintinib PFS curve)	2.8
Committee preferred assumptions (NMA HR applied to digitised RECOURSE and Yoshino PFS curve)	2.5
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	2.5
CORRECT (16)	1.9
CONCUR (17)	3.2
TA866 model predicted value (12)	2.8
Pooled CORRECT and CONCUR (12, 16, 17)	2.1
REBECCA RWE study (18)	2.7
CORRELATE RWE study (19)	2.9
RECORA RWE study (15)	3.1
Trifluridine-tipiracil	
Original Company base case (NMA HR applied to fruquintinib PFS curve)	2.8
Committee preferred assumptions (digitised RECOURSE and Yoshino PFS curve)	2.5
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	2.5
RECOURSE (2)	2.0
TERRA (21)	2.0
Yoshino (3)	2.0
TA405 model predicted value (13)	2.9
Pooled RECOURSE and Yoshino (13)	1.9
Trifluridine-tipiracil monotherapy reported in SUNLIGHT (7)	2.4
Tong 2021 RWE study (22)	3.2
Stavraka 2021 RWE study (20)	3.3
BSC	
Original Company base case (extrapolation of pooled FRESCO and FRESCO data)	1.6

Committee preferred assumptions (NMA HR applied to digitised RECOURSE and Yoshino PFS curve)	1.6
Scenario based on committee preferred assumptions for trifluridine-tipiracil, regorafenib and BSC, and the direct extrapolation of pooled FRESCO and FRESCO data for fruquintinib	1.6
FRESCO (23)	1.8
FRESCO-2 (24)	1.8
Xu, 2012 (25)	1.0
Pooled FRESCO and FRESCO data (26)	1.8
CORRECT (16)	1.7
CONCUR (17)	1.7
Pooled CORRECT and CONCUR (12, 16, 17)	1.8
TA405 model predicted value (13)	1.6
RECOURSE (2)	1.7
TERRA (21)	1.8
Yoshino (3)	1.0
Pooled RECOURSE and Yoshino (13)	1.7

Abbreviations: BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RWE, real world evidence.

Summary

In summary, the updated Company base case is aligned with the Committee's preferred assumptions of:

- Using the extrapolated trifluridine-tipiracil curve as the reference curve
- Applying the NMA hazard ratios for fruquintinib, regorafenib and BSC to the reference curve to derive PFS estimates.
    - After a full assessment of the PH assumption, including further testing requested by the Committee, the Company believe that, on balance, the PH assumption is reasonable between all fruquintinib, regorafenib and trifluridine-tipiracil.

Table 10 presents a summary of the submitted Company base case, the EAG base case, the Committee's preferred assumptions, and the updated Company base case for the estimation of PFS for model comparators. The updated base case results and scenario analysis are presented in Appendix A. Fruquintinib remains dominant vs regorafenib with the updated base case assumptions and additional scenario analysis using independent extrapolations of pooled FRESCO and FRESCO-2 data and is associated with an incremental NHB of [redacted].

Table 10: PFS estimation methods

Treatment	Submitted Company base case	EAG base case	Committee preferred assumptions	Updated Company base case
Fruquintinib	Joint parametric survival model based on pooled FRESCO and FRESCO-2 data	Independent survival model based on pooled FRESCO and FRESCO-2 data	NMA HRs applied to the trifluridine-tipiracil PFS curve	NMA HRs applied to the trifluridine-tipiracil PFS curve
BSC	Joint parametric survival model based on pooled FRESCO and FRESCO-2 data	Independent survival model based on pooled FRESCO and FRESCO-2 data	NMA HRs applied to the trifluridine-tipiracil PFS curve	NMA HRs applied to the trifluridine-tipiracil PFS curve

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	Regorafenib	NMA HR applied to fruquintinib PFS curve	Independent curves fit to digitised KM data from the CORRECT study	NMA HRs applied to the trifluridine-tipiracil PFS curve	NMA HRs applied to the trifluridine-tipiracil PFS curve
	Trifluridine-tipiracil	NMA HR applied to fruquintinib PFS curve	Independent curves fit to digitised KM data from the pooled RECOURSE and Yoshino studies	Independent curve fit to digitised KM data from the pooled RECOURSE and Yoshino studies	Independent curve fit to digitised KM data from the pooled RECOURSE and Yoshino studies

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; KM, Kaplan Meier; NMA, network meta-analysis; PFS, progression-free survival.

7

Dosing

The draft guidance states that the Committee concluded that "*the acquisition cost of fruquintinib should be accurately modelled*" based on the NHS England CDF clinical lead explaining that "*the acquisition cost would be reduced only if a dose of 3mg per day is prescribed*".

Alongside this draft guidance response, the Company have also submitted an enhanced PAS to PASLU for consideration. This is [redacted] Results for the updated base case, including the proposed revised PAS, are presented in Appendix A.

Relative dose intensity

The draft guidance states that the Committee's preferred assumptions include using "*trial-specific relative dose intensity for regorafenib and trifluridine-tipiracil*". However, the Company maintains that using the relative dose intensity (RDI) from the pooled FRESCO and FRESCO-2 data is the most reasonable source of RDI for fruquintinib, regorafenib, and trifluridine-tipiracil in the base case.

Importantly, the definition of RDI varied among the key trials informing the Committee's preferred assumptions for fruquintinib, regorafenib, and trifluridine-tipiracil. The data are therefore not considered comparable and are not considered appropriate to inform RDI in the base case:

- For fruquintinib, in FRESCO and FRESCO-2, RDI was defined as dose intensity (mg/day) / planned dose intensity (mg/day). The planned dose intensity was (5 mg × 21) / 28 = 3.75 mg/day, as per the study protocol. In both the FRESCO and FRESCO-2 studies, drug interruption and cycle delay were not taken into account in the derivation of RDI.
- For regorafenib, cycle delay and dose reduction were factored into the RDI definitions in CONCUR and CORRECT.
- As highlighted by clinical experts at the December 2023 market access advisory board, the RDI of regorafenib would be expected to be lower compared with fruquintinib due to its toxicity profile (5), but it would not be expected to be as low as reported in the CORRECT trial (79.3%). As this includes both dose delay and reduction, this is likely an underestimate of the true RDI when using the same definition as per the FRESCO and FRESCO-2 trials.

- For trifluridine-tipiracil, cycle delay and dose reduction were modelled separately in TA405, as per the data available from the RECOURSE trial:
  - The RDI reported in the RECOURSE trial (89.0%) (2) and the RDI reported in SUNLIGHT (87.3%) (27) are well aligned with the fruquintinib RDI from the pooled FRESCO and FRESCO-2 data (89.6%).

Therefore, applying an equal RDI to all treatments ensures consistency in data informing the analysis across treatments.

This aligns with the Committee-preferred assumptions in TA866 where the pooled CORRECT and CONCUR data were considered the most reasonable source for modelling RDI for both regorafenib and trifluridine-tipiracil, based on a similar evidence base (28):

- The Committee concluded that dose delay and dose reduction should be used to estimate RDI.
- The RDI assumption was supported by RWE that showed similar dose reduction between treatments.
  - Of the identified publications in the SLR, seven RWE studies reported RDI data for regorafenib (29-35). Of these, six studies reported median RDI ranging from 45% to 80% (29-33, 35), and two studies reported mean RDI of 54% to 71% (31, 34). Seven RWE studies reported RDI data for trifluridine-tipiracil. Of these, five studies reported median RDI ranging from 57% to 100% (33, 36-39), one study reported mean RDI of 83% (34), and one study reported the number of participants with median RDI <80% (40), 80 to 100%, 100% or >100%, with the majority reporting median RDI 100%. One RWE study reported median RDI of 85.3% for fruquintinib (41).
- RDI data are only available from CORRECT and RECOURSE for regorafenib and trifluridine-tipiracil, respectively. RDI estimates from pooled trial data for regorafenib and trifluridine-tipiracil are not available as these data are redacted in TA866. Pooled CORRECT, CONCUR and pooled RECOURSE, TERRA and Yoshino data represent the most reasonable source of data for regorafenib and trifluridine-tipiracil, respectively. As this data is not available, and therefore the most reasonable source for RDI for each treatment cannot be used.

The Company agree that more patients would discontinue regorafenib compared with fruquintinib. As per clinical opinion, many patients cannot tolerate regorafenib due to its toxicity profile. However, the impact of patients discontinuing treatment due to unacceptable toxicity is captured within the TTD data in both the CORRECT trial and pooled FRESCO and FRESCO-2 data, which are used to inform time on treatment for regorafenib and fruquintinib in the model base case, respectively.

The Company acknowledge that, due to its toxicity profile, more patients are likely to dose-reduce on regorafenib in clinical practice compared with fruquintinib and trifluridine-tipiracil.. However, the CORRECT RDI is considered to underestimate RDI due to the inconsistency in definition of RDI reported across trials, as discussed above. A scenario has therefore been conducted that explores an RDI for regorafenib that is lower than that of fruquintinib and trifluridine-tipiracil, as presented in Appendix A. This scenario assumes an RDI value of 84.5% for regorafenib, which is the mid-point between the RDI reported in the pooled FRESCO and FRESCO-2 trials and the CORRECT trial. The associated incremental NHB of fruquintinib vs regorafenib is [redacted]. This scenario has a minimal impact on the cost-effectiveness results, with fruquintinib remaining dominant vs regorafenib.

In summary, the Company maintains that it is not reasonable to source RDI from separate sources that define RDI differently, and that it is reasonable to ensure consistency in the data

<table>
<tr><td></td><td>informing base case assumptions. In the absence of better data, the revised Company base case therefore assumes that RDI is equal between comparators, as per the RDI reported in the pooled FRESCO and FRESCO-2 data and the original Company base case. A scenario analysis using a lower RDI value for regorafenib has minimal impact on cost-effectiveness results and is associated with an incremental NHB of fruquintinib vs regorafenib [redacted].</td></tr>
<tr><td>8</td><td>Utility values

The company accepts the Committees preferred approach of using CORRECT utility values in the base case and has explored scenario analysis pooling data from available sources, as requested.

The draft guidance states that “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 CORRECT trial utility values were likely to be a plausible approximation of the pooled estimate”.

Therefore, a meta-analysis was conducted to pool available utility values from the CONCUR/CORRECT, SUNLIGHT and FRESCO-2 trials (Table 11). Both random effects (RE) and fixed effects (FE) models with the inverse variance method for pooling were fitted using reported confidence intervals (CI). The FE models were considered most appropriate for use in the model scenario analysis as per the NMA analysis presented in Section B.2.9 of the Company submission. The values from the CORRECT study alone were excluded from the analysis, as no data on number of observations, standard error (SE) or CI were available, and these data are included the pooled estimates from CONCUR and CORRECT.

Table 11: Utility values from relevant mCRC trials
<table>
<tr><th>Trial</th><th>Progression-free (95% CI), n</th><th>Progressed (95% CI), n</th></tr>
<tr><td>FRESCO-2</td><td>0.71 (0.70, 0.73)
1,455</td><td>0.65 (0.62, 0.69)
326</td></tr>
<tr><td>CONCUR/CORRECT</td><td>0.72 (0.71, 0.73)
2,600</td><td>0.59 (0.56, 0.62)
570</td></tr>
<tr><td>SUNLIGHT</td><td>0.76 (0.73, 0.79)
1,975</td><td>0.68 (0.65, 0.71)
304</td></tr>
</table>
Abbreviations: mCRC, metastatic colorectal cancer.

Results of the FE meta-analysis are presented in Figure 11 and Figure 12, for progression-free and progressed disease, respectively. The utility value for progression-free, 0.72 (95% CI, 0.71, 0.73) and progressed disease, 0.64 (95% CI, 0.63, 0.66), are consistent with the values estimated from FRESCO-2. Results of the RE meta-analysis are presented in Figure 13 and Figure 14.</td></tr>
</table>

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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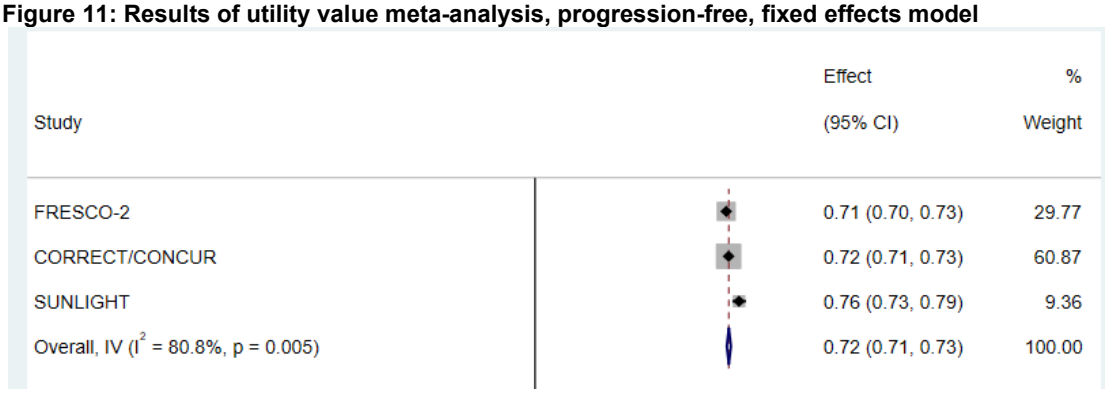
Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 11: Results of utility value meta-analysis, progression-free, fixed effects model

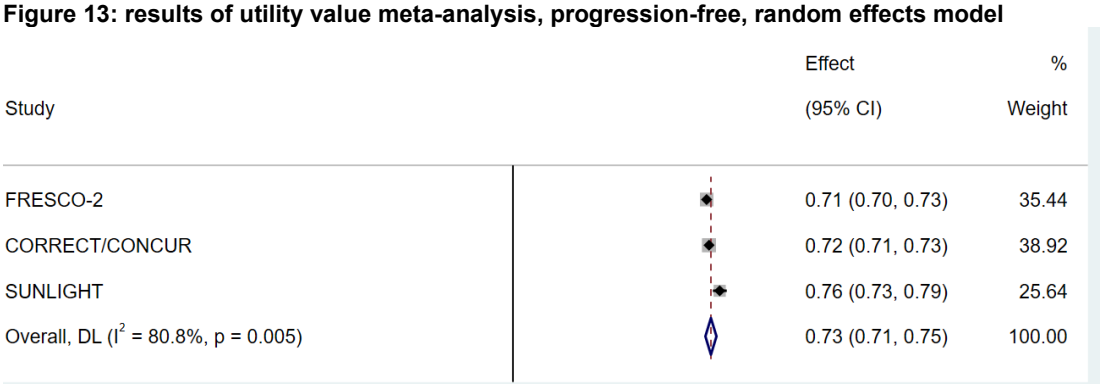


Abbreviations: CI, confidence interval.

Figure 12: Results of utility value meta-analysis, progressed, fixed effects model

Abbreviations: CI, confidence interval.

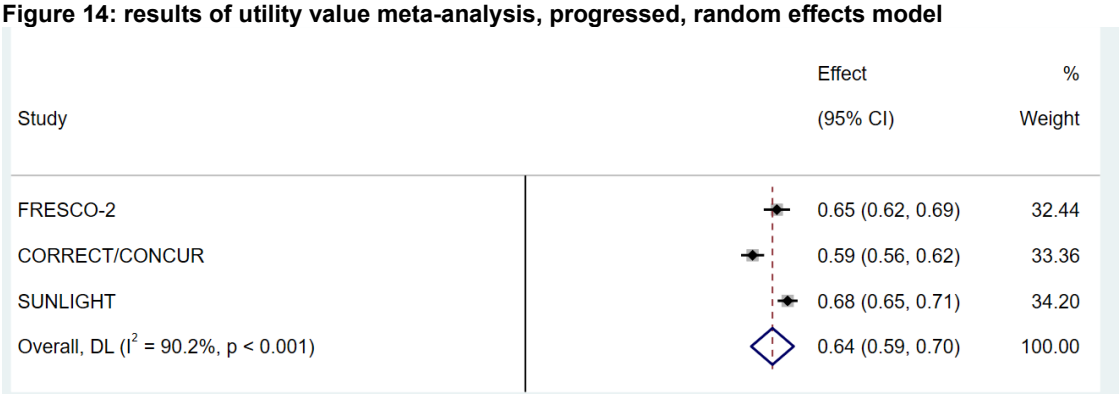
Figure 13: results of utility value meta-analysis, progression-free, random effects model



Abbreviations: CI, confidence interval.

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 14: results of utility value meta-analysis, progressed, random effects model



Abbreviations: CI, confidence interval.

In alignment with the Committee's preferred assumptions, the Company have used utility values from CORRECT in the revised base case. As requested, a scenario using the pooled utility data is also presented (Table 12). The updated base case results and scenario analysis are presented in Appendix A.

Table 12: Updated utility values

Health state	CORRECT (updated base case) (13)	Meta-analysis (scenario)
Progression-free	0.73	0.72
Progressed	0.59	0.64

9

Modelling time-to treatment discontinuation (TTD)

The draft guidance states that the Committee "*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*", and that this approach informs the Committee's preferred assumptions.

The Company considers the Committee's preferred assumption for estimating TTD for regorafenib and trifluridine-tipiracil to be associated with limitations; however, are willing to adopt these assumptions in the updated base case.

Regorafenib TTD

The Committee's preferred approach for regorafenib, which fits an exponential curve through the median TTD reported in the CORRECT trial, assumes a constant risk of discontinuation over time. This assumption is likely to be unrealistic and, as highlighted by the EAG, is simplistic and lacks face validity. In addition, only TTD data from CORRECT were available for regorafenib, and the Committee's preferred approach hence does not align with the clinical data used for OS and PFS (both CORRECT and CONCUR are considered relevant RCTs and inform the NMA).

Furthermore, as highlighted by the Committee in TA866, neither CORRECT nor CONCUR were considered 100% generalisable to the UK (28); the CORRECT trial included only patients that had received prior bevacizumab and may not reflect current clinical practice given that results were first published in 2012. Therefore, using data from both trials as specified in the base case is considered the most robust approach for decision-making, compared with using either CORRECT or CONCUR independently.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

	Importantly, when using the Committee's preferred approach, the predicted mean ([redacted] months) and median ([redacted] months) TTD for regorafenib is lower than that in the CORRECT trial (2.8 and 1.7, respectively). Furthermore, the median TTD from CORRECT (1.7 months) is substantially lower than estimated by clinical experts (2–2.8 months) (5) and RWE data identified in the clinical SLR (2.2–2.5 months) (18, 34). Therefore, the acquisition costs associated with regorafenib may be underestimated in the revised Company base case. **Trifluridine-tipiracil TTD** As only TTD data from RECOURSE and Yoshino were available, the Committee's preferred approach for trifluridine-tipiracil does not incorporate data from the more recent randomised control trial, TERRA. As stated in the response to Comment 10, TERRA was also identified in the SLR and considered a relevant trial to inform a robust network to inform comparative efficacy estimates based on a feasibility assessment. The Committee's preferred approach also does not align with the clinical data used for OS and PFS (21). Furthermore, this approach predicts a median TTD of [redacted] months for trifluridine-tipiracil, which is notably lower than the 3.0 months TTD reported in both recent RWE studies conducted specifically in the UK (20, 22). Whereas the modelled median TTD of [redacted] months predicted using the Company's submitted base case aligns more closely with the median TTD of 2.1 months reported in the recently published NICE TA1008, which assessed trifluridine-tipiracil in combination with bevacizumab (7). This also provides a plausible median TTD estimate that lies between the median TTD estimated by the Committee's preferred approach and reported in the RWE. **Summary** However, in the absence of better TTD data for regorafenib and trifluridine-tipiracil, the Company agree that the Committee's preferred approach is reasonable to inform TTD; these data therefore inform the revised Company base case. The updated base case results and scenario analysis are presented in Appendix A. Table 13 presents a summary of the submitted Company base case, the EAG base case, the Committee preferred assumptions, and the updated Company base case for the estimation of TTD for model comparators.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 13: TTD estimation methods

Treatment	Submitted Company base case	EAG base case	Committee preferred assumptions	Updated Company base case
Fruquintinib	Parametric survival model based on pooled FRESCO and FRESCO-2 data (log-normal distribution)	Independent survival model based on pooled FRESCO and FRESCO-2 data (generalised gamma distribution)	Not stated	Independent survival model based on pooled FRESCO and FRESCO-2 data (log-normal distribution)
Regorafenib	NMA PFS HR applied to fruquintinib TTD curve	Exponential curve fit to the median TTD reported in the CORRECT study	Exponential curve fit to the median TTD reported in the CORRECT study	Exponential curve fit to the median TTD reported in the CORRECT study
Trifluridine-tipiracil	NMA PFS HR applied to fruquintinib PFS curve	Independent curve fit to digitised KM data from the pooled RECOURSE and Yoshino studies	Independent curves fit to digitised KM data from the pooled RECOURSE and Yoshino studies	Independent curves fit to digitised KM data from the pooled RECOURSE and Yoshino studies

Abbreviations: BSC, best supportive care; EAG, external assessment group; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; TTD, time-to-treatment discontinuation.

11

Subsequent treatment

The draft guidance states that the Committee's preferred assumptions include using "*NHS England estimates of subsequent treatment (35%) and a duration of 8 weeks*" to model subsequent treatments.

In the original Company submission, subsequent treatment data from the pooled FRESCO and FRESCO-2 data were used for all comparators. This data aligns with the efficacy data used in the model and was therefore considered the most reasonable source of data. Subsequent therapies were assigned a one week duration, due to the poor survival outcomes for patients with mCRC, and to align with the Committee preferred approach taken in TA866 (28).

The Company are willing to accept the Committee's preferred assumptions where subsequent treatment distributions are based on clinical opinion elicited by the Company (which informed a scenario in the original Company submission), and where NHS England estimates inform the proportion of patients receiving active therapy (35%) and the duration of subsequent therapy (8 weeks). This aligns with the assumptions accepted for decision-making in the recently published NICE TA1008 (7).

A summary of the updated base case assumptions is presented in Table 14. As per the original Company base case, patients in the BSC arm of the model are assumed to receive no further active therapy.

The Company have aligned with the Committee's preferred assumptions in their updated base case, for which results are presented in Appendix A.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 14: Updated subsequent therapy data

Arm	Proportion receiving any subsequent therapy	Regorafenib	Trifluridine-tipiracil
Fruquintinib	35%	0%	100%
Regorafenib	35%	0%	100%
Trifluridine-tipiracil	35%	100%	0%

12

The mean age informing severity modifier calculations

The draft guidance states that the Committee considered two additional severity weighting analyses, but that "*using the SACT data to inform the severity weighting decision was preferable*". This comprised "*using the trifluridine-tipiracil SACT data to estimate mean age (65 years) and to model overall survival*".

Whilst the Company is willing to accept the use of SACT data to model OS, the Company feel a mean age of 65 years may overestimate the mean age of patients who would be expected to receive fruquintinib in NHS practice.

The SACT database informing this mean age (65 years) was collected in patients receiving trifluridine-tipiracil in the UK. The Company does not have information on the dataset itself (e.g. date of data collection period, baseline characteristics), and as a result, is not confident about how reflective it is of current practice. In relation, as described in response to Comment 1, whilst the Company agrees that fruquintinib could be used as a third-line or later treatment, the majority of fruquintinib use is expected to be in fourth-line, which could be slightly different positioning to that of the majority of patients in the SACT data.

Moreover, as discussed in Section B.3.7 of the Company submission, the Company sought validation of the mean age of 59.4 years reported in the pooled FRESCO and FRESCO-2 trials at the UK market access advisory board: clinical experts unanimously agreed that these data were reflective of the population expected to receive fruquintinib in clinical practice (5).

Following receipt of the draft guidance, the Company sought additional feedback via one-to-one discussions with four UK-based oncologists who stated that an increase in early-onset mCRC is being observed in clinical practice (42). The increased diagnosis of early onset mCRC was further mentioned by patient experts at the first NICE Committee meeting for trifluridine-tipiracil with bevacizumab in May 2024 (TA1008) (7). Clinical experts also indicated that the patients receiving active therapy at later lines (as considered in this appraisal) tend to be the younger and fitter patients who are able to tolerate additional lines of therapy and choose to continue with active treatment. Elderly patients are more likely to discontinue active treatment and move to BSC at third-line, such as after their initial chemotherapy, due to tolerability and QoL concerns. Therefore, the average age of patients tends to reduce as patients progress through each line of therapy.

This is pertinent given a mean age of 60 years was accepted in the prior appraisal of regorafenib in the same population (TA866), published in February 2023, which is the most relevant comparator given that the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib (28). While it was acknowledged that there has been an increase in early onset mCRC diagnoses, clinical expert opinion highlighted that there have been no substantial changes to patient demographics since publication of TA866 in 2023, therefore the mean age used in this appraisal remains reasonable.

The Company has also conducted a comparison of age reported by SACT, the pooled FRESCO and FRESCO-2 data, and other RCT data and RWE reported in the literature. The mean age of patients in the pooled FRESCO and FRESCO-2 data also aligns more closely with RWD,

specifically for the use of fruquintinib, which reports a range in median age of 54-61 years (n=271) (43-51). Furthermore, the age of 59.4 years in the pooled FRESCO and FRESCO-2 trials more closely aligns with the RCTs identified in the clinical SLR: the Company considered nine RCTs in the population relevant to this submission (2, 3, 16, 17, 21, 52, 53), and the weighted average of reported median age was 61.1 years (range: 50–64 years).

The Company therefore considers that a mean age of less than 65 years is reasonable to inform the severity modifier calculations in this population, and consider the mean age from pooled FRESCO and FRESCO-2 data (59.4 years) to be the most appropriate value based on clinical expert opinion, the published literature, and precedence in prior NICE appraisals. The associated QALY shortfall analysis summary with updated base case settings is presented in Appendix A.

The Company would like to highlight how sensitive the severity modifier calculations are to mean age. Therefore, whilst the Company acknowledge there is a mismatch between efficacy and mean age, it maintains that it is crucial to accurately and consistently reflect the appropriate age, as per the previous appraisal TA866 and the Phase III clinical trials conducted in the fruquintinib target patient population. For completeness, a scenario using the severity modifier calculations with a starting age of 65 years is also presented in Appendix A. Under the updated Company base case, the proportional QALY shortfall exceeds 0.95 when compared with regorafenib, resulting in a severity modifier of 1.7. In addition, the proportional QALY shortfall exceeds 0.95 when compared with trifluridine-tipiracil and BSC also, resulting in a severity modifier of 1.7 against all comparators.

Factual inaccuracy

The Company have identified a factual inaccuracy in the original submission relating to the number of patients in the FRESCO trial who had previously been treated with trifluridine-tipiracil.

The corrected Table 7 from Document B is provided below. Prior treatment with trifluridine-tipiracil in the FRESCO trial has now been updated from zero patients to 13 (4.7) and 3 (2.2) in the fruquintinib and placebo treatment arms, respectively. The Company would like to apologise for this oversight; however, wants to reassure the Committee that this should not impact decision-making.

Document B, Table 7: Summary of baseline demographics and disease characteristics – FRESCO and FRESCO-2, ITT population

Category	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=138	Fruquintinib + BSC N=461	Placebo + BSC N=230
Age, years				
Mean (SD)	54.3 (10.70)	55.1 (10.53)	62.2 (10.41)	62.4 (9.67)
Sex, n (%)				
Female	120 (43.2)	41 (29.7)	216 (46.9)	90 (39.1)
Male	158 (56.8)	97 (70.3)	245 (53.1)	140 (60.9)
Race, n (%)				
American Indian or Alaska native	0	0	0	1 (0.4)
Asian	278 (100)	138 (100)	43 (9.3)	18 (7.8)
Black or African American	0	0	13 (2.8)	7 (3.0)
Native Hawaiian or other Pacific Islander	0	0	3 (0.7)	2 (0.9)

	White	0	0	367 (79.6)	192 (83.5)
	Other	0	0	5 (1.1)	2 (0.9)
	Multiple races	0	0	2 (0.4)	0
	Not reported/unknown	0	0	28 (6.1)	8 (3.5)
	Ethnicity, n (%)				
	Han Chinese	272 (97.8)	135 (97.8)	0	0
	Non-Han Chinese	6 (2.2)	3 (2.2)	0	0
	Hispanic or Latino	0	0	20 (4.3)	14 (6.1)
	Not Hispanic or Latino	0	0	405 (87.9)	202 (87.8)
	Not reported/unknown	0	0	36 (7.8)	14 (6.1)
	Region and Country, n (%)				
	China	278 (100)	138 (100)	0	0
	North America	0	0	82 (17.8)	42 (18.3)
	Europe	0	0	329 (71.4)	166 (72.2)
	Asia Pacific (Japan and Australia)	0	0	50 (10.8)	22 (9.6)
	BMI (kg/m^2)				
	n	278	138	450	225
	Mean (SD)	23.19 (3.286)	23.52 (3.429)	26.00 (5.159)	25.77 (5.218)
	ECOG PS, n (%)				
	0	77 (27.7)	37 (26.8)	196 (42.5)	102 (44.3)
	1	201 (72.3)	101 (73.2)	265 (57.5)	128 (55.7)
	Time since first diagnosis of CRC (months)				
	n	277[†]	138	461	230
	Mean (SD)	2.24 (1.548)	2.43 (1.788)	52.74 (30.406)	56.02 (28.846)
	Median	1.79	2.04	47.18	49.38
	Min, max	0.1, 9.7	0.3, 9.8	6.0, 242.4	7.1, 154.4
	Stage of CRC at first diagnosis, n (%)				
	Stage I	8 (2.9)	4 (2.9)	20 (4.3)	6 (2.6)
	Stage II	34 (12.2)	18 (13.0)	32 (6.9)	17 (7.4)
	Stage III	118 (42.4)	51 (37.0)	139 (30.2)	84 (36.5)
	Stage IV	117 (42.1)	63 (45.7)	264 (57.3)	119 (51.7)
	Missing	1 (0.4)	2 (1.4)	6 (1.3)	4 (1.7)
	Primary site at first diagnosis, n (%)				
	Colon	147 (52.9)	70 (50.7)	279 (60.5)	137 (59.6)
	Rectum	125 (45.0)	60 (43.5)	143 (31.0)	70 (30.4)
	Colon-rectum	6 (2.2)	7 (5.1)	39 (8.5)	23 (10.0)
	Missing	0	1 (0.7)	0	0
	Primary tumour location at first diagnosis, n (%)				

Left (splenic flexure, descending/transverse /sigmoid colon and rectum)	214 (77.0)	115 (83.3)	335 (72.7)	162 (70.4)
Right (caecum, ascending colon and hepatic flexure)	56 (20.1)	21 (15.2)	97 (21.0)	53 (23.0)
Left and right	4 (1.4)	0	4 (0.9)	2 (0.9)
Unknown	4 (1.4)	1 (0.7)	25 (5.4)	13 (5.7)
Missing	0	1 (0.7)	0	0
Duration of metastatic disease (months)				
n	278	138	461	230
Mean (SD)	18.92 (12.946)	20.57 (14.626)	44.01 (23.978)	46.65 (24.607)
Median	16.03	17.22	37.88	40.97
Min, max	0.9, 79.0	1.9, 81.6	6.0, 192.8	7.1, 147.1
Categories, n (%)				
<18 months‡/≤18 months§	163 (58.6)	75 (54.3)	37 (8.0)	13 (5.7)
≥18 months‡/>18 months§	115 (41.4)	63 (45.7)	424 (92.0)	217 (94.3)
Liver metastases, n (%)				
Yes	185 (66.5)	102 (73.9)	339 (73.5)	156 (67.8)
No	93 (33.5)	36 (26.1)	122 (26.5)	74 (32.2)
***KRAS*‡/*RAS*§ gene status, n (%)**				
Wild type	157 (56.5)	74 (53.6)	170 (36.9)	85 (37.0)
Mutant	121 (43.5)	64 (46.4)	291 (63.1)	145 (63.0)
***BRAF*§ gene status, n (%)**				
Wild type	NR	NR	401 (87.0)	198 (86.1)
V600E mutation	NR	NR	7 (1.5)	10 (4.3)
Other mutation	NR	NR	53 (11.5)	22 (9.6)
Microsatellite/Mismatch repair status, n (%)				
MSS and/or pMMR	NR	NR	427 (92.6)	215 (93.5)
MSI-H and/or dMMR	NR	NR	5 (1.1)	4 (1.7)
Unknown	NR	NR	29 (6.3)	11 (4.8)
Prior use of VEGF inhibitor, n (%)				
Yes	84 (30.2)	41 (29.7)	445 (96.5)	221 (96.1)
No	194 (69.8)	97 (70.3)	16 (3.5)	9 (3.9)
Prior use of EGFR inhibitor, n (%)				
Yes	40 (14.4)	19 (13.8)	180 (39.0)	88 (38.3)
No	238 (85.6)	119 (86.2)	281 (61.0)	142 (61.7)
Prior treatment with EGFR/VEGF inhibitors, n (%)				
No anti-VEGF and no anti-EGFR	167 (60.1)	83 (60.1)	4 (0.9)	5 (2.2)
Anti-VEGF, anti-EGFR or both	111 (39.9)	55 (39.9)	457 (99.1)	225 (97.8)

	Anti-VEGF and no anti-EGFR	71 (25.5)	36 (26.1)	277 (60.1)	137 (59.6)
	Anti-EGFR and no anti-VEGF	27 (9.7)	14 (10.1)	12 (2.6)	4 (1.7)
	Both anti-VEGF and anti-EGFR	13 (4.7)	5 (3.6)	168 (36.4)	84 (36.5)
	Prior treatment with trifluridine-tipiracil and/or regorafenib, n (%)§				
	Trifluridine-tipiracil	13 (4.7)	3 (2.2)	240 (52.1)	121 (52.6)
	Regorafenib	0	0	40 (8.7)	18 (7.8)
	Trifluridine-tipiracil and regorafenib	0	0	181 (39.3)	91 (39.6)
	Number of prior treatment lines				
	Median (Q1, Q3)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	5.0 (4.0, 6.0)	5.0 (4.0, 6.0)
	2 or 3, n (%)	190 (68.3)	98 (71.0)	77 (16.7)	44 (19.1)
	>3, n (%)	88 (31.7)	40 (29.0)	384 (83.3)	186 (80.9)
	Number of prior treatment lines for metastatic disease, n (%)				
	≤3	221 (79.5)	107 (77.5)	125 (27.1)	64 (27.8)
	>3	57 (20.5)	31 (22.5)	336 (72.9)	166 (72.2)

Source: FRESCO final CSR (54), FRESCO tables (55), FRESCO-2 final CSR (56), Dasari et al, 2023 (57).
†Time of first diagnosis was missing for one patient; ‡FRESCO only; §FRESCO-2 only.
Abbreviations: BMI, body mass index; BRAF, v-raf murine sarcoma viral oncogene homologue B; BSC, best supportive care; CSR, clinical study report; CRC, colorectal cancer; dMMR, deficient mismatch repair; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor; ITT, intention-to-treat; KRAS, Kirsten rat sarcoma viral oncogene homologue; MSI-H, microsatellite instability-high; MSS, microsatellite stable; NR, not reported; pMMR, proficient mismatch repair; Q, quartile; RAS, rat sarcoma virus; SD, standard deviation; VEGF, vascular endothelial growth factor.

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Appendix A

Table 15 presents a summary of the updated Company base case, which aligns closely with the majority of Committee preferred assumptions listed in the draft guidance. As described in Comment 13, the updated Company base case also includes a submitted enhanced PAS which, in addition to enhancing the cost-effectiveness of fruquintinib, ensures the acquisition cost of fruquintinib is accurately modelled for people who have a dose reduction.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Table 15: Summary of Company updated base case vs Committee preferred assumptions

Comment	Updated Company base case	Committee preferred assumptions	Alignment between Company and Committee?
Overall survival extrapolation	Trifluridine-tipiracil as the reference curve for OS informed by SACT data • With NMA hazard ratios applied for fruquintinib, regorafenib and BSC • Extrapolated using an average of the log-logistic and generalised gamma curves	Trifluridine-tipiracil as the reference curve for OS informed by SACT data • With NMA hazard ratios applied for fruquintinib, regorafenib and BSC • Extrapolated using an average of the log-logistic and generalised gamma curves	Yes
Progression-free survival extrapolation	Trifluridine-tipiracil as the reference curve for PFS informed by digitised trial data • With NMA hazard ratios applied for fruquintinib, regorafenib and BSC	Trifluridine-tipiracil as the reference curve for PFS informed by digitised trial data • With NMA hazard ratios applied for fruquintinib, regorafenib and BSC	Yes
Time to treatment discontinuation extrapolation	Trifluridine-tipiracil TTD informed by digitised trial data, extrapolated using a log-normal curve • Regorafenib TTD estimated by fitting an exponential curve to median time on treatment	Trifluridine-tipiracil TTD informed by digitised trial data, extrapolated using a log-normal curve • Regorafenib TTD estimated by fitting an exponential curve to median time on treatment	Yes
Utility values	• CORRECT trial utility values (absolute; PF: 0.73, PD :0.59) used • Scenario analysis using a weighted utility value calculated as an average of the CONCUR, CORRECT and SUNLIGHT trials (PF: 0.72, PD: 0.64)	• CORRECT trial utility values (absolute; PF: 0.73, PD:0.59) • Scenario analysis requested using a utility value calculated using a meta-analysis of the CONCUR, CORRECT and SUNLIGHT trials (PF: 0.72, PD: 0.64)	Yes
Relative dose intensity	Equal to fruquintinib for all treatments • Scenario analysis using a lower RDI for regorafenib	Trial-specific	No
Subsequent therapy costs	Subsequent treatment proportions based on clinical opinion, with the proportion of patients receiving active therapy and duration of subsequent therapy informed by NHS England data	Subsequent treatment proportions based on clinical opinion, with the proportion of patients receiving active therapy and duration of subsequent therapy informed by NHS England data	Yes
Mean starting age informing severity modifier calculations	Mean age of 59.4 years (pooled FRESCO and FRESCO-2 data)	Mean age of 65 years (SACT)	No

Abbreviations: BSC, best supportive care; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PF, progression-free; TTD, time to treatment discontinuation.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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A summary of results with the updated base case (pairwise vs regorafenib) are presented in Table 16 and are calculated at the proposed PAS price for fruquintinib as outlined in the response to Comment 7. As noted throughout the original Company submission and this response document, regorafenib is considered the most relevant comparator for decision making. This is based on how the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib, as discussed in Comment 1. Several scenario analyses that are discussed throughout the document are outlined in Table 17 and the scenario results for the comparison vs regorafenib are presented in Table 18. Scenario analyses performed had minimal impact on the incremental NHB of fruquintinib vs regorafenib, with NHB considered to be the most appropriate outcome given the sensitivity of ICER estimates due to small incremental QALYs.

In the base case (including the proposed updated PAS price), fruquintinib was associated with cost savings of [redacted] and an incremental QALY gain of [redacted] vs regorafenib, meaning fruquintinib was dominant when compared with regorafenib. Importantly, fruquintinib also dominates regorafenib in all scenarios. Fruquintinib is associated with an incremental NHB of [redacted] vs regorafenib.

Results are presented using a severity modifier QALY weighting of 1.7. This is in line with calculations of QALY and LY shortfall in the model under the updated base case assumptions, based on a mean age of 59.4 years, as presented in Table 19. The implied severity modifier was assessed for all the scenarios exploring model uncertainty for the fruquintinib and regorafenib comparison described in Table 17. The relevant QALY weighting also remained 1.7 in all scenarios.

The results of these analysis demonstrate that fruquintinib is a cost-effective use of NHS resources, and a positive NICE recommendation for fruquintinib would provide patients and clinicians with a convenient, alternative, oral treatment option with a manageable safety profile, which does not negatively impact quality-of-life, for patients with previously treated mCRC.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Table 16: Base case results (pairwise analysis) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (fruquintinib vs comparator) (£)	Incremental LYG (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator; severity modifier applied)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £20,000 WTP threshold (fruquintinib vs comparator)	Incremental NHB at £30,000 WTP threshold (fruquintinib vs comparator)
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Fruquintinib is dominant	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; NHB, net health benefit.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 17: Summary of scenario analysis

Scenario	Associated comment
Scenario 1: Pooled utility values As requested in the draft guidance, a meta-analysis was conducted to pool available utility values from the CONCUR/CORRECT, SUNLIGHT and FRESCO-2 trials; resulting utility values were applied in this scenario (PF, 0.72; PD, 0.64).	Comment 8
Scenario 2: Independent OS curve for fruquintinib While the Company agree with the Committee's preferred approach to modelling OS, and have adopted this approach in the revised Company base case, this approach may underestimate both the absolute survival and hence the potential absolute survival benefit associated with fruquintinib. In this scenario, OS for fruquintinib is modelled independently and the pooled FRESCO and FRESCO-2 data are extrapolated using a generalised gamma distribution which provided a good statistical and visual fit to the observed data (as discussed in Comment 5). In this scenario, the PH assumption between trifluridine-tipiracil and fruquintinib is relaxed, and the predicted outcomes are more aligned with the observed data.	Comment 5
Scenario 3: Independent PFS curve for fruquintinib While the Company agree with the Committee's preferred approach to modelling PFS, and have adopted this approach in the revised Company base case, this approach may underestimate both the absolute PFS and hence the potential absolute PFS benefit associated with fruquintinib. In this scenario, PFS for fruquintinib is modelled independently and the pooled FRESCO and FRESCO-2 data are extrapolated using a log-normal distribution which provided a good statistical and visual fit to the observed data (as discussed in Comment 6). In this scenario, the PH assumption between trifluridine-tipiracil and fruquintinib is relaxed, and the predicted outcomes are more aligned with the observed data.	Comment 6
Scenario 4: Independent OS and PFS curve for fruquintinib A further scenario is considered in which OS and PFS are both modelled independently for fruquintinib as per Scenario 2 and 3. In this scenario, the PH assumption between trifluridine-tipiracil and fruquintinib is relaxed for both OS and PFS, and the predicted outcomes are more aligned with the observed data.	Comment 5 and 6
Scenario 5: RDI based on mid-point value for regorafenib As discussed in Comment 7, the Company maintains that it is not appropriate to source RDI from separate sources that define RDI differently and that it is reasonable to ensure consistency in the data informing base case assumptions. For completeness, scenario analysis is provided in which an alternative value for RDI is used for regorafenib. This RDI value is lower than that of fruquintinib and trifluridine-tipiracil, and is based on a mid-point between the RDI reported in the pooled FRESCO and FRESCO-2 trials and the CORRECT trial.	Comment 7

Abbreviations: PD, progressed disease; PF, progression-free; PFS, progression-free survival; PH, proportional hazard; OS, overall survival; RDI, relative dose intensity.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 18: Summary of updated scenario analysis results (vs regorafenib) – PAS price

	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £30,000 WTP threshold
Original Company base case	[redacted]	[redacted]	Dominant	[redacted]
Original Company base case (updated PAS‡)	[redacted]	[redacted]	Dominant	[redacted]
Updated Company base case (Table 16)	[redacted]	[redacted]	**Dominant**	[redacted]
Scenario 1: Pooled utility values	[redacted]	[redacted]	Dominant	[redacted]
Scenario 2: Independent OS curve for fruquintinib	[redacted]	[redacted]	Dominant	[redacted]
Scenario 3: Independent PFS curve for fruquintinib	[redacted]	[redacted]	Dominant	[redacted]
Scenario 4: Independent OS and PFS curves for fruquintinib	[redacted]	[redacted]	Dominant	[redacted]
Scenario 5: RDI based on mid-point value for regorafenib	[redacted]	[redacted]	Dominant	[redacted]

†Adjusted with a severity modifier of 1.7 in line with calculations in the model ‡The revised PAS is based on the 5 mg pack for fruquintinib, which is the dose that is used to estimate treatment costs for fruquintinib in the model; comment 7 includes further discussion on the revised PAS.
Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, Net health benefit; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life years.

Severity modifier calculations vs regorafenib

Table 19 and Table 20 present severity modifier calculations vs regorafenib using the Company base case mean starting age from pooled FRESCO and FRESCO-2 data (59.4), and a scenario using the SACT data mean starting age (65), respectively. As per discussion in Comment 12, the Company maintain that the mean age of 59.4 years from the pooled FRESCO and FRESCO-2 data is a reasonable assumption based on clinical expert opinion, the published literature, and precedence in prior NICE appraisals. For completeness, a scenario exploring the relevant severity modifier based on the SACT data mean starting age have been provided.

Methods for calculating the updated severity modifier were as per those described in Section B.3.7 of the Company submission. The resulting absolute and proportional shortfall values were [redacted], and [redacted]% vs regorafenib, respectively, when using a starting age of 59.4. The resulting absolute and proportional shortfall values were [redacted] and [redacted]% vs regorafenib, respectively, when using a starting age of 65. This suggests that a 1.7 x QALY severity multiplier is reasonable across all analyses. Critically, in all scenario analyses conducted that influence QALY estimates, the severity modifier remains 1.7 vs regorafenib, demonstrating the robustness of the severity modifier estimates to changing assumptions.

Table 19: Summary of updated QALY shortfall analysis (starting age of 59.4 years)

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
12.89	Regorafenib: [redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Table 20: Summary of updated QALY shortfall analysis (starting age of 65 years)

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
10.80	Regorafenib: [redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Results vs trifluridine-tipiracil and BSC

For completeness, fully incremental and pairwise results vs trifluridine-tipiracil and BSC are presented in Table 21 and Table 22, respectively. As highlighted in Comment 1 and throughout this response, the relevant comparison for decision-making is fruquintinib vs regorafenib. The comparisons vs trifluridine-tipiracil and BSC is expected to be less relevant for decision-making. Scenario analyses for the comparisons of fruquintinib vs trifluridine-tipiracil and BSC are provided in Table 23.

Table 21: Base case results (fully incremental analysis) – PAS price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs (severity modifier applied)	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	[redacted]	–	–	–	–
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 22: Base case results (pairwise analysis) – PAS price vs trifluridine-tipiracil and BSC

Technologies	Total costs (£)	Total QALYs	Incremental costs (fruquintinib vs comparator) (£)	Incremental LYG (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator; severity modifier applied)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £20,000 WTP threshold (fruquintinib vs comparator)	Incremental NHB at £30,000 WTP threshold (fruquintinib vs comparator)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	–	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; NHB, net health benefit; PAS. Patient access scheme; QALYs, quality-adjusted life years; WTP, Willingness to pay.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 23: Summary of updated scenario analysis results (vs trifluridine-tipiracil and BSC)

	Incremental costs	Incremental QALYs	Pairwise ICER	Incremental NHB
vs trifluridine-tipiracil				
Original Company base case	[redacted]	[redacted]	[redacted]	[redacted]
Original Company base case (updated PAS)	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case (Table 16)	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Pooled utility values	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Independent OS curve for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Independent PFS curve for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Independent OS and PFS curves for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]
vs BSC				
Original Company base case	[redacted]	[redacted]	[redacted]	[redacted]
Original Company base case (updated PAS)	[redacted]	[redacted]	[redacted]	[redacted]
Updated base case (Table 16)	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 1: Pooled utility values	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 2: Independent OS curve for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Independent PFS curve for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 4: Independent OS and PFS curves for fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, Best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PAS, Patient access scheme; PFS, progression-free survival; QALYs, quality-adjusted life year; RDI, relative dose intensity; RWE, real-world evidence.

Severity modifier calculations vs trifluridine-tipiracil and BSC

Table 24 present severity modifier calculations using the Company base case mean starting age from pooled FRESCO and FRESCO-2 data (59.4 years). A scenario was also conducted applying the committee preferred mean age of 65 years from the SACT data, as presented in Table 25. Methods for calculating the updated severity modifier were as per those described in Section B.3.7 of the Company submission. The resulting absolute and proportional shortfall values were [redacted] and [redacted], and [redacted]% and [redacted]% for trifluridine-tipiracil and BSC, respectively, when using a starting age of 59.4 years. The resulting absolute and proportional shortfall values were [redacted] to [redacted], and [redacted]% to [redacted]% for trifluridine-tipiracil and BSC, respectively, when using a starting age of 65 years. This suggests that a 1.7 x QALY severity multiplier is reasonable. Critically, in all scenario analyses conducted which influence QALY estimates, the severity modifier remains 1.7 vs all comparators, demonstrating the robustness of the severity modifier estimates to changing assumptions.

Table 24: Summary of updated QALY shortfall analysis (starting age of 59.4 years)

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
12.89	Trifluridine-tipiracil: [redacted]	[redacted]
	BSC: [redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Table 25: Summary of updated QALY shortfall analysis (starting age of 65 years)

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
10.80	Trifluridine-tipiracil: [redacted]	[redacted]
	BSC: [redacted]	[redacted]

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year.

Appendix B

Following the revised PAS and updated company base case highlighted in Table 15, full sensitivity analysis results from the original Company submission are provided including probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis. Results have been provided for all modelled comparators, however regorafenib is considered the most relevant comparator for decision-making.

Probabilistic sensitivity analysis

A summary of the fully incremental and pairwise probabilistic results is presented in Table 26 and Table 27. Based on the fully incremental probabilistic analysis, BSC is the referent treatment, regorafenib is dominated by both fruquintinib and trifluridine-tipiracil, and fruquintinib is associated with an ICER of £[redacted] per QALY gained vs trifluridine-tipiracil.

In the pairwise probabilistic analysis, fruquintinib is associated with incremental QALYs of [redacted] and cost savings of £[redacted] vs regorafenib and, in line with the deterministic analysis, regorafenib is dominated by fruquintinib. In addition, fruquintinib is associated with incremental QALYs of [redacted] and incremental costs of £[redacted], resulting in an ICER of £[redacted] per QALY gained vs BSC and fruquintinib is associated with incremental QALYs of [redacted] and incremental costs of £[redacted], resulting in an ICER of £[redacted] per QALY gained vs trifluridine-tipiracil.

The probabilistic fully incremental and pairwise ICERs vary slightly vs the deterministic ICERs given the sensitivity of the ICER to small differences in incremental QALYs. However, comparisons of NHB, which do not suffer from this issue, are consistent between the probabilistic and deterministic analyses. Specifically, fruquintinib was associated with incremental NHB at the £51,000 WTP threshold of [redacted], [redacted] and [redacted] vs BSC, trifluridine-tipiracil and regorafenib respectively.

The cost-effectiveness plane for fruquintinib vs the comparators and the CEAC are presented in Figure 15 and Figure 16, respectively. The proportion of simulations considered cost-effective at a WTP threshold of £51,000 per QALY was [redacted]%.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table **26: Base case results, probabilistic sensitivity analysis (fully incremental)**

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
BSC	[redacted]	[redacted]	–	–	–
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	Extendedly dominated
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

Table 27: Base case results, probabilistic sensitivity analysis (pairwise)

Technologies	Total costs (£)	Total QALYs	Incremental costs (£) (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £34,000 (Fruquintinib vs treatment)	Incremental NHB at £51,000 (Fruquintinib vs treatment)
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	Dominated	[redacted]	[redacted]
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	–	–	–	–	–

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, Net health benefit; QALYs, quality-adjusted life years.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 15: Cost-effectiveness plane – fruquintinib PAS price

Abbreviations: BSC, best supportive care; QALYs, quality-adjusted life years.

Figure 16: Cost-effectiveness acceptability curve – fruquintinib PAS price

Abbreviations: BSC, best supportive care; WTP, willingness to pay.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Deterministic sensitivity analysis

Parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by either the 95% CI, or ±20% of the mean value where no estimates of precision were available. Due to the similarity in outcomes between treatments, NHB was recorded at the upper and lower values to produce a tornado diagram.

Results for the 10 most influential parameters are presented in Table 28, Table 29 and Table 30 while the tornado diagrams are presented in Figure 17, Figure 18 and Figure 19, for comparisons against regorafenib, trifluridine-tipiracil, and BSC respectively. The most influential parameters were those associated with the OS and PFS curves for the modelled comparators vs fruquintinib, and the treatment cost of all active treatments. The NHB for fruquintinib vs regorafenib remains positive for all results other than the lower value of the OS HR applied for regorafenib.

Table 28: OWSA results: fruquintinib vs regorafenib

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS HR Fruquintinib vs trifluridine/tipiracil	[redacted]	[redacted]
OS HR Regorafenib vs trifluridine/tipiracil	[redacted]	[redacted]
Cost of regorafenib pack	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
Patient Age	[redacted]	[redacted]
TTD Parametric Fit – fruquintinib – (log-normal Meanlog)	[redacted]	[redacted]
PFS HR Regorafenib vs trifluridine/tipiracil	[redacted]	[redacted]
PFS trifluridine-tipiracil log-normal ln(sigma)	[redacted]	[redacted]
TTD Parametric Fit – fruquintinib – (log-normal SDlog)	[redacted]	[redacted]
Utility: TA405 absolute, progression-free	[redacted]	[redacted]

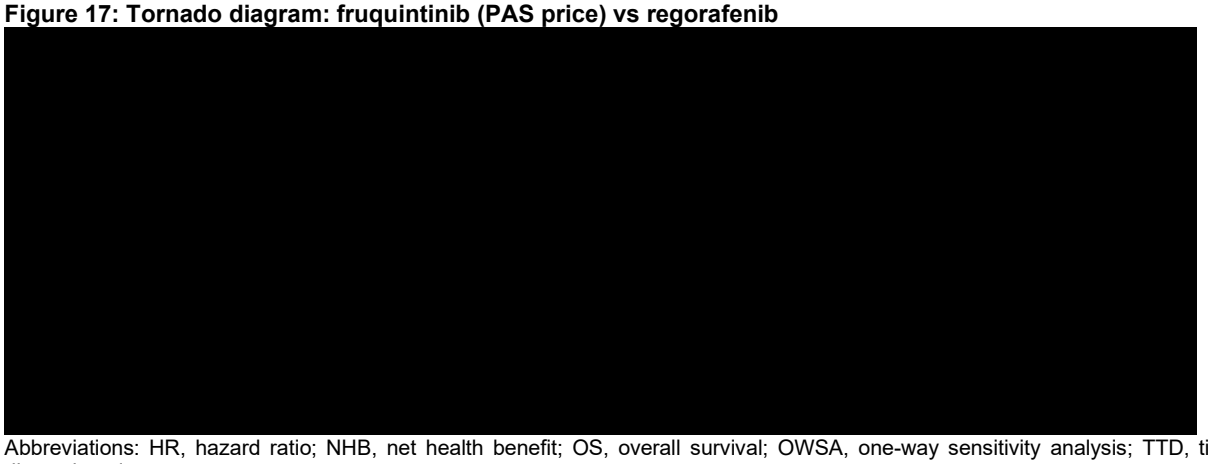
Abbreviations: FE, fixed effects; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; TTD, time to treatment discontinuation.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 17: Tornado diagram: fruquintinib (PAS price) vs regorafenib



Abbreviations: HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; TTD, time to treatment discontinuation.

Table 29: OWSA results: fruquintinib vs trifluridine-tipiracil

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS HR Fruquintinib vs trifluridine/tipiracil	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
Cost of trifluridine-tipiracil pack, 20mg	[redacted]	[redacted]
Cost of regorafenib pack	[redacted]	[redacted]
Mean BSA	[redacted]	[redacted]
TTD Parametric Fit – fruquintinib – (log-normal Meanlog)	[redacted]	[redacted]
Patient Age	[redacted]	[redacted]
TTD trifluridine-tipiracil log-normal constant	[redacted]	[redacted]
Unit Cost: Medical Oncologist Outpatient Visit	[redacted]	[redacted]
TTD Parametric Fit – fruquintinib – (log-normal SDlog)	[redacted]	[redacted]

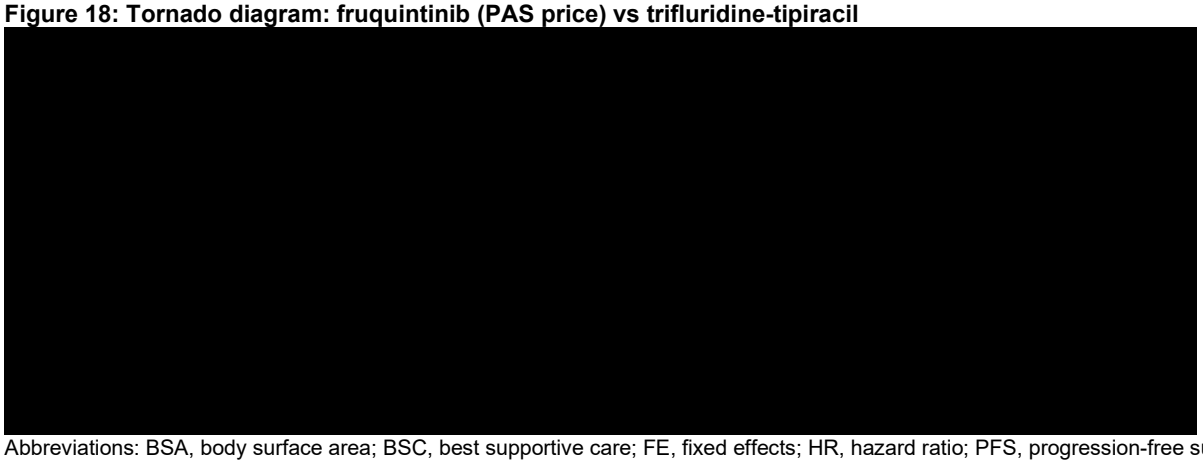
Abbreviations: BSA, body surface area; FE, fixed effects; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 18: Tornado diagram: fruquintinib (PAS price) vs trifluridine-tipiracil



Abbreviations: BSA, body surface area; BSC, best supportive care; FE, fixed effects; HR, hazard ratio; PFS, progression-free survival.

Table 30: OWSA results: fruquintinib (PAS price) vs BSC

Parameter	NHB at lower value of parameter	NHB at higher value of parameter
OS HR Fruquintinib vs trifluridine/tipiracil	[redacted]	[redacted]
OS HR BSC vs trifluridine/tipiracil	[redacted]	[redacted]
Cost of fruquintinib pack, 5mg	[redacted]	[redacted]
Patient Age	[redacted]	[redacted]
TTD Parametric Fit – fruquintinib – (log-normal Meanlog)	[redacted]	[redacted]
Mean BSA	[redacted]	[redacted]
Cost of trifluridine-tipiracil pack, 15mg	[redacted]	[redacted]
Frequency of Resource Use (per 1-Week Cycle) Medical Oncologist Outpatient Visit	[redacted]	[redacted]
Utility: TA405 absolute, progression-free	[redacted]	[redacted]
Frequency of Resource Use (per 1-Week Cycle) Oral Chemotherapy Day-Case	[redacted]	[redacted]

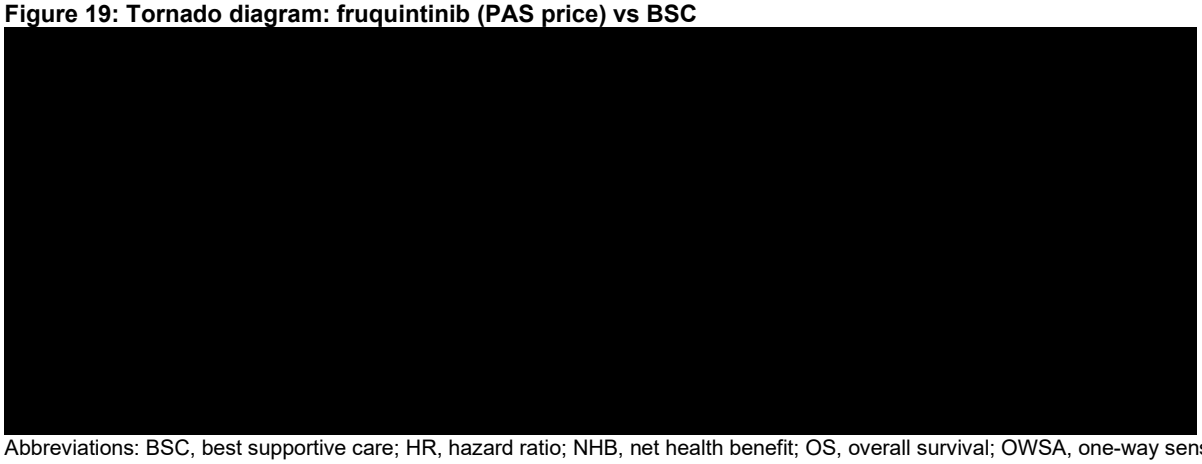
Abbreviations: BSC, best supportive care; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, progression-free survival; TTD, time to treatment discontinuation.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Figure 19: Tornado diagram: fruquintinib (PAS price) vs BSC



Abbreviations: BSC, best supportive care; HR, hazard ratio; NHB, net health benefit; OS, overall survival; OWSA, one-way sensitivity analysis; PFS, Progression-free survival; TTD, time to treatment discontinuation.

Scenario analysis

Scenario analysis is provided for the comparison of fruquintinib with regorafenib, trifluridine-tipiracil and BSC in Table 31, Table 32 and Table 33, respectively. Scenarios run aligned with those reported in the original submission (B3) where possible given the updated base case.

For scenario results of the comparisons of fruquintinib with regorafenib, trifluridine-tipiracil, and BSC, the NHB lay within the range of [redacted] to [redacted], [redacted] to [redacted] and [redacted] to [redacted] respectively, with most scenarios having little impact on the NHB. Fruquintinib remained dominant vs regorafenib in all of the scenarios considered.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 31: Scenario analysis results vs regorafenib (deterministic)

Scenario	Incremental costs	Incremental QALYs (including severity modifier)	Pairwise ICER (fruquintinib vs regorafenib)	Incremental NHB (fruquintinib vs regorafenib)
Base-case	[redacted]	[redacted]	Dominant	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	Dominant	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	Dominant	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	Dominant	[redacted]
Treat to progression	[redacted]	[redacted]	Dominant	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	Dominant	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	Dominant	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2 for BSC arm	[redacted]	[redacted]	Dominant	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	Dominant	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	Dominant	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	Dominant	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	Dominant	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	Dominant	[redacted]
EAG QB2. Random effects NMA	[redacted]	[redacted]	Dominant	[redacted]
EAG QB7. Use mean AE duration data from Pooled FRESCO and FRESCO-2 trials	[redacted]	[redacted]	Dominant	[redacted]
EAG QB9. Use RDI from respective trials	[redacted]	[redacted]	Dominant	[redacted]
EAG QB10. Apply alternative RDI for all treatments	[redacted]	[redacted]	Dominant	[redacted]
EAG QB11. Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	Dominant	[redacted]
EAG QB12. Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Consultation on the draft guidance document – deadline for comments 5pm on 29 October 2024. Please submit via NICE Docs.

Table 32: Scenario analysis results vs trifluridine-tipiracil (deterministic)

Scenario	Incremental costs	Incremental QALYs	Pairwise ICER (fruquintinib vs trifluridine-tipiracil)	Incremental NHB (fruquintinib vs trifluridine-tipiracil)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2 for BSC arm	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB2. Random effects NMA	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB7. Use mean AE duration data from Pooled FRESCO and FRESCO-2 trials	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB9. Use RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB10. Apply alternative RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB11. Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB12. Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life year; TA, technology appraisal.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

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Table 33: Scenario analysis results vs BSC (deterministic)

Scenario	Incremental costs	Incremental QALYs (with severity modifier)	Pairwise ICER (fruquintinib vs BSC)	Incremental NHB (fruquintinib vs BSC)
Base-case	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 0% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Discount rate 1.5% for Costs and outcomes	[redacted]	[redacted]	[redacted]	[redacted]
Time Horizon 5 years	[redacted]	[redacted]	[redacted]	[redacted]
Treat to progression	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 AEs excluded	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments: 2 week duration	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent treatments from Pooled FRESCO and FRESCO-2	[redacted]	[redacted]	[redacted]	[redacted]
Resource use: based on clinical opinion	[redacted]	[redacted]	[redacted]	[redacted]
Exclude concomitant medications	[redacted]	[redacted]	[redacted]	[redacted]
Grade 1-2 disutility as per Grade 3 for clinically identified AEs	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA866	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease utility decrement: TA405	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB2. Random effects NMA	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB7. Use mean AE duration data from Pooled FRESCO and FRESCO-2 trials	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB9. Use RDI from respective trials	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB10. Apply alternative RDI for all treatments	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB11. Subsequent therapy proportions from clinical opinion + 10% of patients receiving subsequent therapy	[redacted]	[redacted]	[redacted]	[redacted]
EAG QB12. Subsequent therapy duration: 4 weeks	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality-adjusted life year; TA, technology appraisal.

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Servier Laboratories ltd

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	Servier feels strongly that with regards to the RDI for regorafenib, there needs to be consistency across appraisals, especially with TA1008. Therefore, we agree with the committee that the trial-specific relative dose intensities should be applied and that the acquisition cost of should be accurately modelled. In TA1008, the committee preferred an

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Draft guidance comments form

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	analysis that more closely matched regorafenib's use in clinical practice, which likely includes dose reductions in line with CORRECT
2	Servier are unsure how a severity modifier of 1.7 should be applied. This does not seem plausible when in TA1008, in both the company's and the EAG's updated base cases, the QALYs generated from the company model implied a 1.2 weighting for the comparisons with both trifluridine–tipiracil alone and regorafenib. As this is looking at the same disease area, in the same line of treatment, this appears to be inconsistent that 2 different weightings are used across appraisals. Servier considers this may be due to the low age in FRESCO which is younger than the age in RWE
3	Servier question the differences in its clinical trials including previous treatment history and ethnicity. The FRESCO trial included only people in China, differences in the trials might affect whether it was appropriate to pool the studies. The FRESCO-2 study appears to be more appropriate, although these people were more heavily pre-treated and therefore only applicable to the 4th line population. Therefore Servier is concerned about the generalisability to earlier lines of treatment. We would like to highlight that based on table 7 page 48, the "median prior treatment lines were 3 (2;4) in FRESCO and 5 (4;6) in FRESCO 2. Only 16.7% had 2 or 3 prior lines in FRESCO 2 in the fruquintinib arm while 83.3% had more than 3 lines" confirming clinical evidence in a contemporary population in later lines. Also, in FRESCO 2, 52% of the fruquintinib group received FTD-TPI and 39% received both FTD-TPI and regorafenib, hence 91% receiving trifluridine-tipiracil prior to fruquintinib, owing to evidence in that setting post trifluridine-tipiracil and/or regorafenib. PH tests show a violation in FRESCO making it less robust to pool FRESCO and FRESCO-2, especially given that being pre-treated with TAS & regorafenib could be an effect modifier.
4	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. Servier agree with this as the committee for TA1008 noted that the SACT data was an optimal source for validating OS because: the number of people in the dataset was very large (n=6,170), the data was mature, with longer-term follow up for more people at the tail of the curve, the data came directly from NHS practice in England, so was generalisable to the target mCRC population in NHS clinical practice. Again, for consistency, Servier feels this should be used.
5	Servier is concerned that the submitting company has assumed that treatment discontinuation was proportional between treatments and constant over time. This is unlikely because the treatments have different adverse event profiles. Regorafenib, in particular, would probably have a higher initial discontinuation rate than the other treatments, as heard in this appraisal and also in TA1008.
6	Servier agree that post-progression treatment duration of 1 week was unlikely to be plausible. In TA1008, Patients were assumed to receive subsequent treatments for a mean duration of 2 months, which was in line with clinical opinion received and used in a previous mCRC in NICE submission (TA668).
7	With regards to the safety study on EAERs, Servier feels it is important to mention that adverse events should not only be assessed by frequency but also by their impact on QoL. While neutropenia is well managed today, skin adverse events like hand-foot syndrome can be severe enough to significantly disturb patients and necessitate dose adjustments, affecting both QoL and optimal anticancer treatment. In addition,this is a

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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	naïve comparison, not accounting for differences in trial design, patient populations, data collection methods, and timing that may differ significantly.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal 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 provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**I was on the original NICE review and am responding as a clinical advisor to this committee.**

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	**Direct – financial** **I have been involved in 4 Takeda ad boards:** **Sep 23 - £2516.25** **Oct 23 - £1525** **Dec 23 - £2135** **Feb 24 - £1220** **Indirect** **I received a fee for a talk for BAYER at UK Oncology Forum in June 23 (£1912.50).** **Over the last 3 years I have received payment from Servier for lectures, meetings and to attend international meetings. Since April 2020, I have had 12 such meetings receiving £17,500** **GSK advice on survey** **Dec 23 - £580** **MSD ad board** **Nov 22 - £1680** **None of these are on-going**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**No links to the tobacco industry.**
Name of commentator person completing form:	**Prof Mark Saunders** **Consultant Clinical Oncologist** **The Christie** **Manchester** **M20, 4BX**

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that **……..In the NICE draft guidance, you ask four questions. I have addressed them in that order below.**
1	**Has all of the relevant evidence been taken into account?** At the time it probably was. But as you state in section 3.3 (comparators), this has now changed after the release of the positive guidance for the use of trifluridine-tipiracil and bevacizumab (TT/BVZ). This has quickly taken the 3rd line position for the treatment of patients with MCRC. Therefore, we are realistically trying to determine which type of care / treatment should be given in the 4th line setting. The reason for selecting TT/BVZ in the 3rd line setting is because the OS for this combination is significantly greater than for regorafenib or fruquintinib. There will be occasions when the latter two drugs would be considered more appropriate than TT/BVZ in the 3rd line setting, but these scenarios would be rare. I know fruquintinib has a licence for 3rd line use, BUT, it is very unlikely to be used in this setting in the vast majority of patients due to TT/BVZ being more efficacious. In the 4th line setting there will be 3 options. Presently we have regorafenib and best supportive care (BSC). If fruquintinib is added to this list, then the new comparators for the agent under review, are regorafenib and BSC. It is important to compare fruquintinib to BSC since by 4th line setting, probably only 10-20% of the patients originally treated for MCRC will be alive and have an acceptable performance status (PS) to allow this. If we compare fruquintinib to regorafenib in terms of efficacy, I accept it is similar. BUT, if you compare the two drugs toxicity profile, then fruquintinib is the much better tolerated drug (you have data to show this). So, given this scenario, the best 3rd line treatment is TT/BVZ. The best 4th line treatment should be BSC or fruquintinib. There will be so few patients suitable for 5th line treatment (estimate 5%) that I think regorafenib will not be used in addition to fruquintinib. Regorafenib will fall out of favour because of its poor toxicity profile compared to fruquintinib which is equally effective but much better tolerated. So, to answer your question, NO, all of the evidence has NOT been taken into consideration. This NEW evidence is: 1. the recent availability of TT/BVZ in the 3rd line setting, 2. the better toxicity profile of fruquintinib compared to regorafenib 3. and finally, the need to compare to it to BSC in the 4th line setting.

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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2	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** I totally accept the need to look at the long-term outcomes of any drug and try to extrapolate this data from existing survival curves. However, long term survival just isn't likely in the situation under consideration. If what I have said in 1) above is accepted, then we only need to consider fruquintinib in the 4th line setting. The survival advantage of fruquintinib over BSC is in the terms of 2 months. Outside a clinical trial, when patients are of worse PS, this will mean patients may live 4-5 months rather than 2-3 months in the 4th line setting. The numbers living 1 year will be extremely small and the numbers living 2-3 years can be confidently predicted as virtually nil. So, to try to extrapolate to a few years is a completely unrealistic scenario.
3	**Are the recommendations sound and a suitable basis for guidance to the NHS?** Because of what I have said in 1) and 2) above, I don't think they are.
4	**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?** No
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
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- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

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without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Single Technology Appraisal

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Role	N/A
Other role	N/A
Organisation	N/A
Location	N/A
Conflict	N/A
Notes	No
Comments on the DG:	

- Has all of the relevant evidence been taken into account? Yes
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? No
- Are the recommendations sound and a suitable basis for guidance to the NHS? NO
- 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? No

It is curious that committee have disregarded the accepted gold standard method for the assessment of treatment in this clinical scenario - the randomised placebo trial in favour of a a complex analysis based on a series of questionable assumptions.

Name	[redacted]
Role	N/A
Other role	N/A
Organisation	N/A
Location	N/A
Conflict	N/A
Notes	No
Comments on the DG:	

Has all of the relevant evidence been taken into account?
We have concerns that the relative merits of one drug versus another have not been taken in to account adequately, The clinical community are quite

clear that there would be a preference for the use of fruquinitinib over the currently available option of regorafenib. There are evident challenges of cross trial comparison but fruquintinib supercedes regorafenib in all key clinical and patient based outcomes.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
The challenges of the modelling approaches and their extrapolation to 10 years in therapies that offer a modest additional survival advantage are as always fraught with errors and biases. It is quite clear that a number of the models might potentially fit. It is however, challenging that a model was obtained for regorafenib that saw its approval in the same setting, whilst, with a better drug to the opinion of all expert groups the model does not produce a similar result. Surely if this is the case then some further negotiation over cost per person per cycle of therapy becomes a highly relevant point to explore

Are the recommendations sound and a suitable basis for guidance to the NHS?
Our concern as indicated in 2 are that this will not appear “sound” to the clinical and patient community given the approval of other drugs in this setting, with no greater benefit and better patient tolerability

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?
None

Name	[redacted]
Role	N/A
Other role	N/A
Organisation	N/A
Location	N/A
Conflict	N/A
Notes	No
Comments on the DG:	

Has all of the relevant evidence been taken into account?
I have 2 major concerns as regards this.

Firstly, the combination of trifluridine–tipiracil with bevacizumab was not considered as a comparator. This was stated in the guidance, as it was going through NICE appraisal at the same time. This is now available across the UK, and has very rapidly become the de facto third-line treatment of choice for metastatic colorectal cancer. While not compared head-to-head in a clinical trial with fruquintinib, the efficacy and safety profile mean that this will be used as the standard care 3rd-line treatment

for approximately 90% of people with metastatic colorectal cancer. A few people will have contra-indications to bevacizumab but not to trifluridine–tipiracil, and these contra-indications may also extend to fruquintinib which is in the same class of anti-angiogenics as bevacizumab. Another few people may wish to have oral only treatment. Some people will be enrolled onto a clinical trial, but will then have the same choices on progression of their disease after they finish on the trial. Due to the NICE approval of trifluridine–tipiracil with bevacizumab, the true comparator for fruqintinib is in the fourth-line not third-line setting for the vast majority of patients.

Secondly, given the comparators used, I do not think that the committee have adequately listened to the clinical community or to the patient representatives involved. Colorectal oncologists across the UK are very clear that they would always use fruquinitinib if it were available rather than regorafenib. While not compared head-to-head in a clinical trial with either regorafenib or trifluridine–tipiracil, the evidence base is clear from the 3 trials that compared these drugs plus best supportive care to placebo plus best supportive care. Fruquintinib had better response rates, disease control rates, progression-free survival and overall survival. Fruquintinib also had significantly less toxicity than regorafenib, and the toxicity burden in comparison to trifluridine–tipiracil is similar overall (albeit with differing details base don their mechanisms of action).

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
I have 2 major concerns as regards this.

Firstly, the challenges of the modelling approaches and their extrapolation to 10 years in therapies that offer a modest additional survival advantage in the palliative third-line setting and beyond are very major. There are multiple differing errors and biases when making a (relatively arbitrary) choice of which model seems to fit best. The sad truth is that the median overall survival with all 3 agents is in the region of 6.0 – 7.5 months, with only one quarter to under one half of patients alive at 12 months in the 3 trials. Prolonged survival out beyond 3 years is exceedingly unlikely.

Secondly, the models that NICE used which resulted in approval of both trifluridine–tipiracil and regorafenib in the third-line and beyond setting should clearly be out-performed by fruquntinib given its superior efficacy compared to these two other agents. If the issue in fact comes down to one of drug costs alone, then this should be discussed in commercial confidence again with Takeda.

Are the recommendations sound and a suitable basis for guidance to the NHS?
As above, neither the clinical nor patient communities believe that these recommendations are a sound and a suitable basis for guidance to the NHS. This is due to the clinical trial and real world evidence of the efficacy and safety of fruquintinib in third-line and beyond in multiple countries and populations, particularly in comparison to regorafenib and trifluridine–tipiracil

monotherapies which are already approved in the third-line and beyond setting in metastatic colorectal cancer.

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?
No

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Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

EAG CRITIQUE OF COMPANY RESPONSE TO ACD

CONFIDENTIAL

Produced by **Aberdeen HTA Group**

Authors: Dwayne Boyers[1]
David Cooper[2]

1 Health Economics Research Unit, University of Aberdeen, UK
2 Aberdeen Centre for Evaluation, University of Aberdeen, UK

Date completed: **06 November 2024**

Version: **1.0**

Correspondence to: Dwayne Boyers
Senior Research Fellow
Health Economics Research Unit
University of Aberdeen, UK
Email: d.boyers@abdn.ac.uk

Strictly confidential: Contains [redacted] information

1 Overview

This document provides the EAG's brief commentary and critique of the company's submitted response to the appraisal consultation document (ACD), ahead of the second appraisal committee meeting for the NICE technology appraisal of Fruquintinib for previously treated metastatic colorectal cancer [ID6274]. The commentary/critique provided below should be read in conjunction with the company's submitted response to the ACD.

A confidential appendix to this report provides a full set of results presented in this document and the company ACD response, applying confidential price discounts for comparators and subsequent treatments used in the economic model.

The company provided a revised economic model and updated set of base case analyses in response to the appraisal consultation document to align with the preferences outlined by the committee following ACM1. This document describes the EAGs view of the additional analyses provided and focuses on remaining areas of uncertainty / disagreement between the company and committee preferred preferences. Where appropriate, additional EAG commentary is provided on the company's approach taken to address committee queries and additional analysis requests.

Issues 1 & 2 Treatment pathway and relevant comparators

Patients eligible for trifluridine-tipiracil plus bevacizumab

Following a positive NICE recommendation for trifluridine-tipiracil plus bevacizumab in the third line plus setting (TA1008), the company note that fruquintinib would most likely be used in the 4th line setting unless patients were unable or unwilling to have treatment with trifluridine-tipiracil plus bevacizumab. The company suggest that trifluridine monotherapy would therefore no longer be an appropriate comparator at 4th line, and that the only relevant remaining comparator for fruquintinib at 4th line or later is regorafenib.

The EAG understands the company's rationale and agrees that the positive recommendation from TA 1008 likely moves fruquintinib to 4th line or beyond in UK clinical practice for patients who are suitable for trifluridine-tipiracil plus bevacizumab. The EAG also agree that trifluridine-tipiracil would not be a relevant comparator in this clinical setting, given that patients would already have received it as part of combination therapy. However, the EAG believes that at 4th line or beyond, BSC may also be a relevant comparator for some patients, particularly those who had previous treatment with or were otherwise unsuitable for regorafenib due to tolerability concerns.

Given that fruquintinib would likely be used in the 4th line treatment setting post TA1008 recommendations also has implications for the most appropriate clinical parameters to include in the economic modelling. For example as noted in EAG documentation prior to the first AC meeting, data from the FRESCO 2 study might be more generalisable to the UK population most likely to receive fruquintinib treatment at 4th line than the pooled FRESCO and FRESCO 2 data. Whilst there would be a clear advantage in using the FRESCO 2 study to inform fruquintinib's effectiveness (OS and PFS) at later lines of treatment, this would substantially reduce the volume of data available to inform decision making. The EAG explored the potential to provide a scenario analysis using only the FRESCO-2 data in the economic model, but are concerned that the current model functionality does not support its full integration. For example, HRs applied for fruquintinib to the committee preferred SACT dataset do not update when switching between fruquintinib data source. Further adaptation to the model would therefore be required to generate robust results using FRESCO-2 study data only for fruquintinib.

Patients not eligible for trifluridine-tipiracil plus bevacizumab

The company considers regorafenib to be the most appropriate comparator for fruquintinib in the third line setting where patients are not eligible, or unable to have trifluridine-tipiracil plus bevacizumab. The company note that due to only a very small proportion of patients receiving trifluridine-tipiracil monotherapy in this setting, it is not a relevant comparator.

The EAG are unclear as to why the company believes regorafenib, as opposed to trifluridine-tipiracil monotherapy would be the treatment of choice in this scenario. There may be patients who are ineligible for combination treatment due to the bevacizumab component, or may be unwilling to attend the hospital appointments for administration, and in these cases, the EAG considers that trifluridine-tipiracil monotherapy would also be a relevant comparator. Furthermore, trifluridine-tipiracil monotherapy may be preferred over regorafenib unless it was previously used earlier in the treatment pathway due to regorafenib's toxicity concerns. The EAG therefore believes that both trifluridine-tipiracil monotherapy and regorafenib are relevant comparators in the 3rd line setting for patients who are unable or unwilling to have trifluridine-tipiracil plus bevacizumab treatment. Should the committee wish to take a view that trifluridine-tipiracil plus bevacizumab is not yet standard UK clinical practice, given the recency of the TA1008 recommendations, the EAG again believes that both trifluridine-tipiracil monotherapy and regorafenib should be considered as appropriate 3rd line comparators.

Issue 3 NMA results

The EAG's opinion is that any improvement in overall survival from fruquintinib in comparison to regorafenib or trifluridine-tipiracil is small in magnitude. The Company's use of numerical improvement implies a larger but non-significant difference. The EAG would either retain the existing phrase in the draft guidance or consider rephrasing to a small improvement. The EAG acknowledges that the NMA results show a significant benefit from fruquintinib in comparison to both regorafenib and trifluridine-tipiracil for PFS and a significant benefit for both OS and PFS in comparison to BSC and placebo. The EAG view on proportional hazards assumptions are discussed in issues 5 and 6 below for OS and PFS respectively.

The EAG note the company's arguments that PFS should be prioritised as an outcome over OS, both the EAG view is that both are relevant for decision making. Both PFS and OS contribute to the economic modelling and hence are relevant considerations for estimating QALY gains from fruquintinib and comparators. Given time restrictions for the EAG critique of the company response to the ACD, it has not been possible for the EAG to seek independent clinical advice around the company's argument that PFS should be prioritised over OS for decision making.

Issue 4 NMA subgroup results

The EAG are satisfied that the company's response is appropriate. The EAG agree that the "no prior anti-VEGF" subgroup is too small to provide an informative analysis and that the position of fruquintinib in the treatment pathway would reduce the relevance of the subgroup.

Issue 5 & 6 Overall and progression free survival extrapolation

The EAG are broadly satisfied with the company's approach of applying hazard ratios derived from the NMA to the trifluridine-tipiracil reference OS curves derived from the SACT dataset. However, there remains some uncertainty as to whether the PH assumptions hold true. The EAG agree with the Company that NICE TSD 14 suggests inspection of cumulative hazard plots and the global test of Schoenfeld residuals are the recommended methods for assessing the PH assumption, but the results of the various tests poing to uncertainty in the validity of the PH assumption. Table 1 summarises the analyses performed by the company to determine whether or not the proportional hazards (PH) assumption holds for OS and PFS.

Table 1: Proportional Hazard Assumptions summary for OS and PFS

		Log-cumulative hazard plot inspection		Global test of Schoenfeld residuals		Interaction tests with time and log-time	
		OS	**PFS**	**OS**	**PFS**	**OS**	**PFS**
Original submission	Comparison of fruquintinib and BSC.	"Relatively parallel" and curves do not cross	Cross RDIat the start. "Relatively parallel"	Reject PH assumption	Reject PH assumption	N/A	N/A
Response to draft guidance	Comparison of fruquintinib and trifluridine-tipiracil	"Relatively parallel over time"	"Converge towards the end of the follow-up period when the number of patients at risk is reduced. Comparable for the majority of the time period and relatively parallel over time."	PH assumption is not rejected	PH assumption is not rejected	Both tests suggest the association between treatment effect and outcomes is not independent of time	Both tests suggest the association between treatment effect and outcomes is not independent of time

The EAG note that the global test of Schoenfeld residuals rejected the PH assumption for the comparison of fruquintinib vs. BSC and that the log-time interaction tests suggest that the association between treatment effect and outcomes is not independent over time for the comparison with trifluridine-tipiracil. The EAG would therefore have liked to see results of sensitivity analyses using an alternative modelling approach such as a time-partitioned model, using fractional polynomial or piecewise approaches as suggest in the ACD. Providing these analyses would have provided further evidence as to whether relaxing the PH assumption would have an important impact on the ICER in the economic model. The EAG note that the company has provided scenario analyses using independently fitted curves to fruquintinib and trifluridine-tipiracil data. The EAG accepts that this approach relazes the PH assumption and allows for extrapolations closely aligned with the observed data. However, the EAG also accepts that this approach fails to make full use of all randomised evidence. The EAG would further point out that the company's use of independently fitted curves only applies to trifluridine-tipiracil and fruquintinib, not to regorafenib. This would be a further source of uncertainty.

Issue 7 Dosing & RDI

The EAG is satisfied that the company's response to the query on dosing is robust, but does not believe that the decision to apply equal RDIs to all treatment arms is appropriate. The EAG has not been able to identify sufficient data that would enable a re-calculation of the RDIs using exactly the same methodology across all studies. However, the EAG's clinical expert opinion was that the RDI for regorafenib should be substantially lower than that for fruquintinib and trifluridine-tipiracil, which would align with the EAG preferred approach based on the available trial data. The EAG also note that the reported RDIs for fruquintinib and trifluridine-tipiracil are broadly similar ([redacted] and 89.0% respectively). This would suggest that any differences in calculation approach across studies would only have had minimal impact on the calculated values. Whilst the EAG acknowledges some uncertainty, we retain our preferred base case assumption that treatment specific RDIs should be used to inform treatment acquisition costs in the economic model.

Issue 8 Health state utility values

Section 3.14 of the ACD requested additional analyses exploring pooled utility values from existing evidence and previous NICE appraisals in the mCRC space. The company has

provided the results of both a fixed and random-effects meta analysis to pool health state utility values across the FRESCO-2 study, CORRECT/CONCUR (available as pooled only), and SUNLIGHT studies. HSUVs are provided for progression free and progressed health states. The revised company base case utilises the CORRECT study utility values as used in TA866 and applies the pooled data from the fixed effects meta analysis as a scenario analysis.

The EAG consider the company's approach to pooling health state utility values to be appropriate, aligned with committee preferences from the ACD (Section 3.14) and helpful for decision making. The EAG are satisfied that using a fixed-effects model is justified. Furthermore, the FE and RE models generate very similar point estimates of health state utility values and the decision about which model to use would have little impact on the ICER.

The EAG and company preferred base case assumptions post ACD are aligned. Data from the CORRECT study (progression free = 0.73; progressed = 0.59) are preferred for the base case analysis because they align closely with the population currently receiving treatment in UK NHS practice (i.e. trifluridine-tipiracil monotherapy). This is important because it ensures that utility source and length of life components for QALY calculation are derived from a similar population.

The EAG are concerned that the utilities derived from the SUNLIGHT trial are substantially higher than compared to other appraisals, particularly in the progressed population. Given that fruquintinib will now most likely be used as 4th line therapy, it may be more appropriate to use the lower overall values from TA405 for decision making, as opposed to using the higher FRESCO-2 or TA1008 utility values, which might over-estimate quality of life in the further progressed population where fruquintinib would most likely be used. This approach would also maintain alignment with NICE's preference from the TA1008 appriasal of trifluridine-tipiracil plus bevacizumab.

Issue 9 Time to treatment discontinuation

The EAG and company preferred base case analyses are aligned with the NICE ACD (Section 3.11) for time to treatment discontinuation modelling for trifluridine-tipiracil and regorafenib. The preferred approach uses a LN curve fitted to digitised TTD data from the

RECOURSE and Yoshino trials for trifluridine tipiracil and an exponential curve fitted to the median from the CORRECT trial for regorafenib.

The EAG were unclear as to what the committee's preferred assumption was for the modelling of fruquintinib time to treatment discontinuation data from Section 3.11 of the ACD. The EAG preferred to use the generalised gamma model, where as the company have used a log-normal model fitted to the pooled FESCRO and FRESCO-2 data.

Issue 10 Subsequent treatments

The company have updated their base case analysis to include 35% of the post progression population receiving subsequent treatments, for a treatment duration of 8 weeks.

The EAG are satisfied that the company's revised approach is aligned with the committee preferred assumptions from the ACD. However, it is important to acknowledge that the subsequent treatment distribution might be affected by the acceptance of trifluridine-tipiracil plus bevacizumab at 3rd line treatment. For example, if patients have previously received trifluridine-tipiracil monotherapy as part of combination therapy at 3rd line, they might be less likely to be challenged with it again post progression on fruquintinib. Regorafenib might be a more appropriate consideration in this scenario if patients were fit enough to receive the treatment. The EAG has explored a scenario where 100% of patients progressing on fruquintinib receive trifluridine-tipiracil and are satisfied that this assumption is not a major driver of the ICER given the relatively short duration of treatment post progression.

Issue 11 Mean age for severity weighting calculations

The company noted a concern that the mean age of participants in the SACT dataset (age 65) might be an over-estimate of the mean age of participants who would likely receive fruquintinib in UK clinical practice. They draw several sources of evidence to support this case, specifically:

A) The company argue that because fruquintinib is more likely to be used as a 4th line therapy, the mean starting aghe may be different to the starting age in the SACT dataset. They have consulted clinical experts who advised that patients receiving later lines of treatment are likely to be younger and fitter on average than those receiving earlier lines of treatment.

B) The company point to existing clinical trial evidence (n=9 studies) showing that the weighted average of reported median ages was 61.1.
C) The company also note that a mean age of 60 was used for the previous appraisal of regorafenib (TA866), who the company argue is the most relevant comparator for this assessment.

The EAG acknowledge the company's concerns, but are not satisfied that the case is sufficiently strong to apply a starting age this is misaligned with the overall survival estimates from the SACT data. The EAG's main concern with applying a mean starting age from a source that is different to the population used to calculate absolute life year gains is that those life year gains (i.e. overall survival) might not be applicable in a younger age group. Applying the OS curves to a younger age group could under-estimate total remaining life years in that younger age group. The EAG therefore prefers to maintain consistency between the mean starting age and the OS curves derived from the SACT data for calculating QALY severity weightings for use in the economic model.

Whilst the EAG note the company's logic, there may also be equally valid counter-arguments to support the use of an older mean starting age compared to the trial data. For example:

A) Going forward, fruquintinib will most likely be used post trifluridine-tipiracil plus bevacizumab, meaning that patients will have progressed through additional treatments which prolong progression free time. It could be argued that such patients would be older because they've had additional lines of treatment.
B) The EAG notes the company's argument about median age of 60 in other RCT studies, but mean ages could feasibly be older than medians in those studies and so 60 might be an underestimate. The EAG has not had sufficient time to cross check the reported baseline age in all studies prior to submission of this critique.
C) The mean age of 60 considered in previous decision making was based on evidence available to the committee at the time of making those decisions. The EAG believes the committee would not have had access to the SACT data for those decisions.

On balance, whilst the EAG notes and appreciates the company concerns, we retain the view that the mean age from the SACT data are appropriate for calculating severity weightings.

QALY gains under the company and committee preferred base case analyses post ACD are aligned. The only disagreement relates to the most appropriate age for calculating the severity weighting. Table 2 below compares the calculated severity weighting for both age inputs (company preferred age 59, and SACT data age 65). The York QALY shortfall calculator is used for severity weighting calculation to main consistency across appraisals (QALY Shortfall Calculator). The severity weighting applied is a function of age, gender and remaining QALYs in the current standard of care (assumed to be trifluridine-tipiracil monotherapy derived from the SACT dataset). The EAG note that in both cases, a severity weighting of x1.7 applies. However, it should be noted that the severity weighting is sensitive to both the utility values used in the base case analysis and the preferred OS extrapolation curve, and this sensitivity is great at a starting age of 65 than at 59. For example, when using a starting age of 65, applying a log-logistic curve to the SACT OS data reduces the severity weighting for comparisons against trifluridine-tipiracil to x1.2. Similarly, using pooled utilities from the fixed effects meta analysis, would also reduce the severity weighting to x1.2 for all comparisons except BSC.

Table 2: Severity weighting for trifluridine-tipiracil monotherapy (Company vs. EAG base case post ACM1)

	Company base case post clarification	**SACT data**
Age	59*	65***
Proportion female	42%	42%**
Remaining discounted QALYs (tri-tip)	[redacted]	[redacted]
Absolute shortfall	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]
Severity weighting	X1.7	X1.7

* Age rounded to nearest whole number

**Assumption – The EAG does not have access to the gender breakdown. However, this is unlikely to make a difference to the weighting applied

*** Age is the age at commencement of the first line of treatment that contains trifluridine-tipiracil in the SACT dataset.

Issue 12 Company identified factual inaccuracy

The EAG note the company's amendment to Table 7 of the original company submission. The EAG would like to thank the company for providing the corrected table and are satisfied that there are no important implications for decision making.

Results

All results of cost-effectiveness analyses are provided in a confidential appendix to this critique document that includes confidential cPAS and CMU prices for comparator and concomitant treatments costed in the economic model.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274] – Company response to Committee's requests following ACM2

7th April 2025

Dr Charles Crawley and NICE technical team
Chairman, Committee B, National Institute for Health and Care Excellence

Re. Company response to Committee requests following the second Appraisal Committee Meeting (ACM2) for fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Dear Dr Charles Crawley,

The Company would like to thank the Evaluation Committee for their consideration on this appraisal. The Company would like to emphasise that they are keen to collaborate with the National Institute for Health and Care Excellence (NICE) to ensure that a positive recommendation can be made for fruquintinib and hope that the additional information provided below in response to analysis requests after ACM2 will support the NICE Committee to achieve this.

Takeda communicated to NICE via email on 10th January 2025 that they considered the extent of the additional analyses requested by the Committee at this late stage, following the second appraisal committee meeting (ACM2) on 12th December 2024, to be unreasonable. However, Takeda acknowledge the Committee's response (30th January 2025) and are pleased to hear that the Committee also do not wish to delay patient access in an area of high unmet need. To demonstrate Takeda's ongoing commitment and flexibility to ensure patients most in need gain access to fruquintinib, Takeda have agreed to explore all the analyses as per the Committee's response on 30th January 2025.

The Company have updated their base case to further align with the Committee's preferences:

- Conducting further analyses to confirm whether proportional hazards (PH) hold and updating network meta-analysis (NMA) analyses using fractional polynomials (Request 3)
- Using utility values sourced from the pooled fixed effects analysis for 3L+ (Request 4)
- Accepting the Committee's preferred assumption regarding treatment-specific relative dose intensity (RDI) estimates from the relevant clinical trials for all treatments (Request 5)
- Updating mean starting age as per the systemic anti-cancer therapy (SACT) data (Request 6)

The Company have also provided further scenario analyses as per the Committee's requests:

- Presenting scenario results for populations by line of treatment (3L+ vs 4L+) (Request 1)
- Presenting scenarios with different comparators by line of treatment (Request 2)
- Using utility values sourced from FRESCO-2 for 4L+ (Request 4)
- Using regorafenib as the reference curve in the 4L+ scenario (Request 7)
- Keeping all other assumptions as per the draft guidance
- Updating severity modifier calculations using these preferences (Request 8)

The results for the requested analyses are presented in Appendix A.

Crucially, across the Committee requested scenario analyses and the updated Company base case (Appendix B), which incorporates all of the Committee's preferred assumptions but one (splitting by 3L+ and 4L+), fruquintinib remains dominant vs regorafenib which is considered to be the key comparator, with a stable incremental net health benefit (NHB). The severity modifier also remains 1.7x in all scenarios. Takeda are aware that a confidential patient access scheme (PAS) simple discount is in place for regorafenib and believe that fruquintinib is cost-effective at a willingness-to-pay (WTP) threshold of £25,000 per QALY vs regorafenib.

To further reduce uncertainty in this conclusion, Takeda have submitted an enhanced patient access scheme (PAS), which has been accepted by Patient Access Scheme Liaison Unit (PASLU). This is [redacted]

Fruquintinib for previously treated metastatic colorectal cancer [ID6274] – Company response to Committee's requests following ACM2

[redacted]. This demonstrates the Company's flexibility and commitment to reaching a positive outcome for patients with metastatic colorectal cancer (mCRC).

Together with the additional analyses requested and conducted at draft guidance stage, Takeda believe that these serve to extensively explore any uncertainties in the fruquintinib evidence base, and trust this is sufficient to alleviate any of the Committee's remaining concerns to reach a positive recommendation for fruquintinib.

Yours sincerely,

[redacted]

Senior Health Economics Manager, Oncology
Takeda UK Ltd.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

Company response to the Committee's requests following ACM2

Request number	Comments
1	**Splitting the population by line of treatment (third-line plus [3L+] vs fourth-line plus [4L+])** As communicated throughout the appraisal, the clinical community has consistently expressed a preference for maintaining clinician and patient choice and flexibility with as broad a recommendation as possible for fruquintinib, in line with its marketing authorisation. As per expert clinical opinion at ACM2, fruquintinib has potential for broad use from 3L onwards, and any optimised recommendation would be heavily discouraged, given the restriction this would impose on clinician and patient choice in an area of high unmet need. Flexibility in prescribing is particularly important in this later-line population, given the lack of clinical guidelines on sequencing of available and emerging treatments. Furthermore, the pooled FRESCO and FRESCO-2 trial data used throughout this appraisal encompasses patients across the broader 3L onwards population, and clinicians agreed that this is representative of UK clinical practice. The Company therefore do not consider it appropriate for the Committee to consider the results of the two populations separately to make independent recommendations at 3L+ and 4L+. The Company maintain that the majority of fruquintinib use is expected to be after trifluridine-tipiracil in combination with bevacizumab, replacing current use of regorafenib (i.e. in the 4L+ setting), and agree with the Committee that a small proportion (<10%) of patients will not be suitable for treatment with trifluridine-tipiracil in combination with bevacizumab at 3L and will therefore be eligible for treatment with fruquintinib in this setting (3L). However, the Company encourages the Committee to consider that there may be a very small number of patients who are eligible for treatment with trifluridine-tipiracil in combination with bevacizumab but choose not to receive this therapy. Reasons could include the desire to seek a break from chemotherapy, given residual chemotherapy side effects, such as myelosuppression and cytopenia, from patients' intensive 1L and 2L treatment may limit the suitability or desire for further chemotherapy treatment such as trifluridine-tipiracil (1). Additionally, patients or clinicians may prefer to explore therapies with alternative modes of action or methods of administration, for example by choosing an all-oral regimen to minimise trips to the hospital, rather than choosing treatment with bevacizumab which would require regular intravenous infusions. Based on the marketing authorisation, these patients are eligible to receive fruquintinib at 3L too. While the Company emphasise that this is a very small number of patients (and hence trifluridine-tipiracil in combination with bevacizumab is not considered a relevant comparator), it would be considered restrictive to clinician and patient choice to optimise the broad 3L onwards population to patients with mCRC who are ineligible for trifluridine-tipiracil in combination with bevacizumab only. Based on this, the Company encourage the NICE Committee to provide a recommendation in line with the marketing authorisation of fruquintinib to avoid limiting patient and clinician choice (2). Nevertheless, as the Company are keen to ensure that all the Committee's requests are addressed, scenarios for the 3L+ and 4L+ populations have been presented. Updated assumptions for the 3L+ base case include: • Fractional polynomial NMA hazard ratios (HRs) applied vs. trifluridine-tipiracil reference curve (SACT for OS and pooled RECOURSE and Yoshino for PFS) (3) • Utility values sourced from the pooled fixed effects analysis • Treatment-specific RDI estimates • Updated mean starting age as per the SACT data for 3L patients (64.30 years) Updated assumptions for the 4L+ scenario include: • Fractional polynomial NMA HRs applied vs (a) regorafenib reference curve (CORRECT trial) and (b) fruquintinib reference curve (FRESCO-2 trial) in separate scenarios (4, 5) • Utility values sourced from the FRESCO-2 trial (4)

Company response to the Committee's requests following ACM2

	• Treatment-specific RDI estimates • Updated mean starting age as per the SACT data for 4L patients (64.70 years) All other assumptions remain as per the base-case 3L+ population. The results of the analysis split by line are presented in Appendix A. The incremental NHB vs regorafenib for the 3L+ and 4L+ scenarios is similar across scenarios ([redacted] vs [redacted] in the 3L+ and 4L+ (FRESCO-2 reference curve) populations, respectively). The difference in results is mostly driven by the choice of reference curve. This is discussed in response to Request 3.
2	**Relevant comparators differ by line of treatment** As detailed in Request 1, the Company have provided the requested analyses for the 3L+ and 4L+ populations separately, however, maintains that an unrestricted 3L+ population is most appropriate for decision making. The Company maintains that the most relevant comparator for this appraisal is regorafenib, both when considering an unrestricted 3L+ population and when splitting by line (3L+ and 4L+ scenarios). ***3L+*** The Committee has requested analyses where trifluridine-tipiracil monotherapy and regorafenib are the relevant comparators for the 3L+ analysis. The Company and Committee are aligned that the treatment landscape is evolving and that trifluridine-tipiracil monotherapy use in 3L is expected to be rapidly replaced by trifluridine-tipiracil in combination with bevacizumab following the publication of a positive recommendation for NICE TA1008 in August 2024 (6-9). As fruquintinib is not expected to replace use of trifluridine-tipiracil in combination with bevacizumab, it has been confirmed by the Committee that trifluridine-tipiracil in combination with bevacizumab is not a relevant comparator for this appraisal. As confirmed by clinical experts, a small proportion (<10%) of patients will not be suitable for trifluridine-tipiracil in combination with bevacizumab at 3L, for example if they have progressed quickly on earlier fluorouracil-based chemotherapy or are immunosuppressed, and it is expected that the majority of these patients would instead currently receive regorafenib at 3L (10). It is expected that fruquintinib will replace this current use of regorafenib in the 3L setting and therefore, the Company consider that regorafenib is the most relevant comparator vs fruquintinib. As discussed in Request 1, there may be a very small number of patients who are not eligible for bevacizumab or choose to avoid bevacizumab, who may currently choose to receive trifluridine-tipiracil monotherapy. The Company acknowledge that there may be the odd patient who may choose to receive fruquintinib at 3L as opposed to trifluridine-tipiracil monotherapy. However, the number of patients for whom this may be relevant is so small that the Company do not consider a comparison of fruquintinib vs trifluridine-tipiracil monotherapy to be relevant for decision making. ***4L+*** The Committee has requested analyses where regorafenib and BSC are the relevant comparators for the 4L+ analysis. The vast majority of patients will receive trifluridine-tipiracil in combination with bevacizumab at 3L+ and thus the only current active therapy available for these patients after progressing, at 4L+ is regorafenib. It is expected that fruquintinib will replace this current use of regorafenib in the 4L+ setting and therefore, the Company consider that regorafenib is the most relevant comparator vs fruquintinib. Currently, in the very small proportion of patients who are not suitable for treatment with trifluridine-tipiracil with bevacizumab and progress on a 3L treatment, patients receive either regorafenib or best supportive care (BSC) at 4L, depending on prior treatment. Given fruquintinib is expected to replace treatments currently used at 3L in this population, it is expected that these patients would not be treated with fruquintinib at 4L+. The Company do, however, acknowledge that there may be a very

Company response to the Committee's requests following ACM2

	small number of patients who do not receive fruquintinib at 3L and therefore may be eligible for fruquintinib at 4L+ in the place of BSC. Given the small patient numbers under consideration, the comparison with BSC in this 4L setting is therefore considered less relevant for decision-making. In summary, the Company maintain that the most relevant comparison for decision making is a pairwise comparison vs regorafenib. Nevertheless, the Company have addressed the Committee's request and presented pairwise comparisons vs regorafenib and trifluridine-tipiracil at 3L+ and vs regorafenib and BSC at 4L+. In addition, based on the Committee's preferred assumptions, a weighted ICER has been estimated to reflect the expected use of fruquintinib in the real-world. Full results of the Committee's requested analysis are presented in Appendix A. The updated base case results are presented in Appendix B. Based on the committee's requested analyses, fruquintinib remains dominant compared with regorafenib.
3	**If proportional hazards doesn't hold then time-varying modelling is required** After ACM2, the Committee requested time and treatment group interaction tests between fruquintinib and BSC based on the pooled FRESCO and FRESCO-2 data (11). As previously discussed, the Company consider there to be limitations in the tests of the interaction between treatment group and time requested by the Committee: • These tests are not recommended in NICE Decision Support Unit technical support document (DSU TSD) 14 (12). • Too many interaction terms risks overfitting to the data, where the model captures random noise rather than the underlying relationships within the data (13). • Studies are typically under-powered for this type of assessment, and the test may be inappropriate if its functional form is not specified correctly. The Company therefore consider other approaches that are recommended in the NICE DSU TSD 14 such as the log-cumulative hazards and global test of proportional hazards (PH) previously presented, to be a more robust assessment of the PH assumption. The interaction between time and treatment group, and between log-time and treatment group, was significant for overall survival (OS) and progression-free survival (PFS) ($p<0.05$), suggesting that the association between treatment effect and outcomes is not independent of time and therefore, that the PH assumption may not hold (Table 1, Table 2, Figure 1 and Figure 2). **Table 1: Time and treatment group interaction tests, fruquintinib vs BSC, pooled FRESCO and FRESCO-2 data, OS** | | HR (95% CI) | p-value | |---|---|---| | Interaction with time | 1.02 (1.009, 1.03) | <0.001 | | Interaction with log-time | 1.672 (1.339, 2.088) | <0.001 | Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; OS, overall survival.

Company response to the Committee's requests following ACM2

Figure 1: Time and treatment group interaction, fruquintinib vs BSC, pooled FRESCO and FRESCO-2 data, OS

Abbreviations: BSC, best supportive care; HR, hazard ratio; PH, proportional hazards; OS, overall survival.

Table 2: Time and treatment group interaction tests, fruquintinib vs BSC, pooled FRESCO and FRESCO-2 data, PFS

	HR (95% CI)	p-value
Interaction with time	1.035 (1.011, 1.06)	0.036
Interaction with log-time	1.582 (1.183, 2.115)	0.002

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 2: Time and treatment group interaction, fruquintinib vs BSC, pooled FRESCO and FRESCO-2 data, PFS

Abbreviations: BSC, best supportive care; HR, hazard ratio; PFS, progression-free survival; PH, proportional hazards.

Company response to the Committee's requests following ACM2

	The Company appreciate that the plots and interaction tests suggest that the PH assumption may not hold for OS or PFS, however reiterate that other approaches are more suitable for assessing the PH assumption and, on balance, evidence suggests there is no strong evidence to suggest that PH does not hold. Regardless, to ensure all Committee requests are adequately addressed, the Company have provided an updated NMA using fractional polynomials that relaxes the PH assumption. **Fractional polynomial NMA** In order to address Committee Request 3, a time-varying NMA analysis was conducted, and hazard functions for all treatments were modelled using fractional polynomials (FP). The methods and results for this additional NMA are detailed below. The FP NMA has been incorporated into the Company base case, which demonstrates Takeda's flexibility to reducing uncertainty in the modelling assumptions and commitment to achieving a positive recommendation for patients with mCRC in this area of high unmet need. Importantly, the cost-effectiveness results of the FP NMA show that relaxing the PH assumption should no longer be a decision-limiting factor in this appraisal, with fruquintinib remaining dominant vs the key comparator regorafenib in both the 3L+ and 4L+ scenarios. Furthermore, using the FP NMA as opposed to the constant HR NMA improves the cost-effectiveness of fruquintinib vs regorafenib in both the 3L+ and 4L+ scenarios. The Company therefore believes that this analysis reduces the uncertainty in assumptions around relative efficacy in the model. **Fractional polynomial time-varying HR NMA methodology** In line with the constant HR Bayesian NMAs described in full in the original Company submission (Document B.2.9 and Appendix D), eight RCTs were included in the FP NMA, utilising direct evidence from all treatments compared with placebo ± BSC (hereafter referred to as BSC). A summary of studies and the accompanying network diagram can be found in Table 16 and Figure 17 of the original Company submission, respectively. The analyses were conducted in OpenBUGS (version 3.2.3), using the BRugs package in R and were aligned with the methodologies outlined in Jansen 2011 (14). **Data structure** The data structure for conducting FP NMA requires survival outcome data to be divided up into multiple consecutive time intervals, such that the following data are available for each trial. This enables the hazard rate during all time intervals to be estimated for an individual treatment: • Number of events during each time interval (progression or death [PFS] or death [OS]) • Number of patients at risk at the start of each time interval. For the fruquintinib trials, these data were available from the IPD, however for the comparator studies, pseudo-IPD were generated by digitising published KM curves for each treatment arm. Digitising software, WebPlotDigitizer (15, 16), was used to extract the comparator data, and the algorithm published by Guyot et al. 2012 (17) used to re-create the IPD. From the pseudo-IPD, the number of events and number of patients at risk for each time interval, could be estimated. **Choice of time intervals for aggregating data** The IPD/pseudo-IPD were aggregated into 1-month time intervals: 0–1 months; 1–2 months; 2–3 months etc. for inclusion in the FP NMA. Data for the individual time intervals were derived for months 1 through 25 of follow-up for PFS and months 1 through 31 for OS. One challenge that can be encountered with FP NMA is preferential model fitting to those trials that have the longest follow-up; however, in the current dataset, this is not anticipated to be a significant problem as although there are differences in follow-up times between trials, the vast majority of events (survival likelihood going to zero or near-zero) are observed for all included studies during the NMA follow-up period (25 months for PFS and 31 months for OS).

Company response to the Committee's requests following ACM2

Fractional polynomial model

The FP approach estimates hazards for each treatment and HRs for each treatment comparison, which vary over time. As stated in Jansen 2011 (14), the first order FP for a hazard at time *t* of a two-arm RCT comparing treatment B with treatment A can be presented as follows:

$$\ln(h_{kt}) = \beta_{0k} + \beta_{1k}t^{p} \text{ with } t^{0} = log(t) \quad \text{(Eqn 1)}$$

$$\begin{pmatrix}\beta_{0k}\\ \beta_{1k}\end{pmatrix} = \begin{cases}\begin{pmatrix}\mu_0\\ \mu 1\end{pmatrix} \; if \; k = A\\ \begin{pmatrix}\mu_0\\ \mu_1\end{pmatrix} + \begin{pmatrix}d_0\\ d_1\end{pmatrix} \; if \; k = B\end{cases} \quad \text{(Eqn 2)}$$

where h_{kt} reflects the hazard with treatment *k* at time *t*. The vector $\begin{pmatrix}\mu_0\\ \mu 1\end{pmatrix}$ reflects the parameters β_0 and β_1 of the 'baseline' treatment A, whereas the vector $\begin{pmatrix}d_0\\ d_1\end{pmatrix}$ reflects the difference in β_0 and β_1 of the log hazard curve for treatment B relative to A. The parameter d_0 corresponds to the treatment effect with a proportional hazard model. Under the proportional hazard assumption, d_1 equals 0. If $d_1 \neq 0$, d_1 reflects the change in the log HR over time. Hence, by incorporating d_1 in addition to d_0, a multi-dimensional relative treatment effect is used rather than a single parameter for the relative treatment effect. For a second order FP, the equation is extended to:

$$\ln(h_{kt}) = \beta_{0k} + \beta_{1k}t^{p1} + \beta_{2k}t^{p2}$$

and in the special case that $p_1 = p_2 = p$, the model becomes a 'repeated powers' model, defined as:

$$\ln(h_{kt}) = \beta_{0k} + \beta_{1k}t^{p} + \beta_{2k}t^{p}log(t).$$

A variety of FP models were tested to determine which combination of polynomials had the best fit across studies. Fractional polynomial models were fitted with one or two parameters of different powers selected from the following standard set of powers: S = (-2, -1, -0.5, 0, 0.5, 1, 2, 3), in line with recommendations and the approach taken in other published analyses (14, 18-20). In addition, -3 was also considered as this has been suggested as potentially useful when survival probabilities change rapidly close to time=0 (18). With options for nine different powers, this resulted in nine first-order and 54 second-order models.

Fixed-effect and random-effects models and model priors

Both fixed-effects (FE) and random-effects (RE) models were conducted. To avoid over-parameterisation in the RE model, heterogeneity was modelled across the intercept (i.e. the non-time-varying effect of treatment) and assumed non-varying effects of time within each treatment. Non-informative priors were used for both mean hazards and treatment effects. As defined by Jansen 2011 (14) (equation 9 of the publication), these non-informative priors were defined as a multivariate normal distribution, with mean vectors centred at 0, and covariance matrices with diagonals of 10,000, and off diagonal elements of 0.

Model diagnostics and criteria for model selection

The model selection for the best fit model was based on the assessments proposed by Petersohn 2023 (20), as follows, to identify the most appropriate model(s):

- Model convergence was checked through inspection of trace plots and the ratios of Monte-Carlo error to the standard deviations of the posteriors; ratio values greater than 5% are strong signs of convergence issues (21). Models that did not converge were eliminated from further model selection assessments.
- Statistical goodness of fit was assessed by ranking deviance information criteria (DIC) for converged models. A model with a lower DIC is generally preferred, with a difference of more than three points considered to provide meaningful differentiation between the model fits. The three models that provided the best statistical fit based on DIC were considered in the further model selection assessments described in steps (3-5): this was considered a pragmatic approach given time restraints on conducting these analyses.

- The hazards over time were assessed for face validity: models that appeared to overfit the data (i.e., when extreme hazards or outliers in HRs are predicted by the model) or predict implausible trends in hazards over time (implausible curve crossing between treatments in terms of hazards) were considered poor model choices.
- The predictive accuracy of models was evaluated by overlaying predicted survival curves with observed KM data and assessing visual fit.
- The face validity and clinical plausibility of the modelled hazard rates and long-term survival were assessed by comparing predicted outcomes (long term survival curves, median PFS/OS, and landmark statistics) with the observed data, published RWE and clinical opinion. Models that predicted implausible trends over time (survival curves crossing between treatments), or predicted extrapolated outcomes that do not reflect external long-term evidence or clinical expert opinion were considered poor model choices.

Strengths and limitations of the FP approach

The primary strengths of this analysis include the maturity of the OS and PFS data from the studies included in the NMA. All time-dependent NMAs suffer from the danger of unreasonable long-term projections even when there is excellent fit to the observed data (20). In the current analyses, most studies were able to observe all PFS events that would occur in the group of patients receiving BSC and the majority of events in the group receiving the treatment of interest. The studies also observed the majority of both BSC and treatment of interest events for OS. That said, the shapes of the curves are primarily driven by the places in the observation window for which there is the most data – here, the first 5 months for PFS and the first 9 months for OS. The tail ends of these curves suffer from both low event rates and more censoring, meaning that survival projections in the tails are highly uncertain and are likely more dependent on behaviour in the early part of the curves than they are the actual data in the tails. Thus, while early differences are likely more trustworthy to interpret, given they are based on more events, later differences are harder to interpret as a small number of additional events in one treatment arm may impact the overall conclusion.

Results and goodness of fit assessment

Progression-free survival

Statistical goodness of fit

The DIC statistics for the nine first-order and 54 second-order models, along with model convergence as described previously, were explored. The top fitting models are presented in Table 3 for PFS. DIC statistics for all FE and RE models are reported in Appendix C, Table 21 and Table 22, respectively.

Table 3: Top fitting models – Investigator-assessed PFS

P1	P2	Dbar	Dhat	pD	FE_DIC	FE_rank	Dbar	Dhat	pD	RE_DIC
-3	-3	1209	1176	32.59	1241	1	1203	1168	35.6	1239
-3	-2	1236	1203	33.13	1269	2	1230	1194	35.91	1266
-2	-2	1271	1238	32.8	1303	3	1265	1228	36.34	1301

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effect; P1, 1st Power; P2, 2nd Power; PFS, progression-free survival; pD, leverage (effective number of parameters); RCT, randomised controlled trial; RE, random-effects.

The top fitting models by DIC are aligned between the FE and RE models. For both FE and RE analyses, functions of time that included $1/time^3$ (-3, -3) offered the best fit.

These three models that provided the best statistical fit based on DIC were considered in further model selection assessments; this was considered a pragmatic approach given time restraints on conducting these analyses. This also aligns with the approach that was taken in TA997 (pembrolizumab with chemotherapy in adenocarcinoma) which was considered acceptable by NICE (22).

Company response to the Committee's requests following ACM2

Face validity of hazards over time

The FE and RE provided similar DIC statistics for each model (within three points), and the hazards over time were comparable across models. As RE models are associated with challenges regarding the lack of statistical heterogeneity in PFS found between trials in the direct meta-analysis, and in general, parsimonious models are preferred, the FE models were considered for further model fit assessments. This was considered reasonable given the time limitations on completing these analyses. Plots of hazards over time for the RE models are presented in Appendix C.

For the best-fitting FE FP NMA models for PFS by DIC, hazards were estimated in the model across a lifetime time horizon, by extrapolating the respective beta coefficients (presented in Appendix C). The face validity of the predicted hazards over time was assessed. Plots of hazards over time for the (-3, -2), (-3, -3) and (-2,-2) models are presented in Figure 3, Figure 4 and Figure 5, respectively.

Figure 3: PFS hazards over time, FE (-3, -2)

Abbreviations: BSC, Best Supportive care; FE, fixed-effect; Fruq, fruquintinib; PFS, progression-free survival.

Company response to the Committee's requests following ACM2

Figure 4: PFS hazards over time, FE (-3, -3)

Abbreviations: BSC, Best Supportive care; FE, fixed-effect; Fruq, fruquintinib; PFS, progression-free survival.

Figure 5: PFS hazards over time, FE (-2, -2)

Abbreviations: BSC, Best Supportive care; FE, fixed-effect; Fruq, fruquintinib; PFS, progression-free survival.

On visual inspection of the hazards over time, the shape of the hazards for each treatment is similar across all explored models. In all models, fruquintinib demonstrates favourable PFS hazards vs all comparators in the initial period of up to ~5 months, considered to reflect the time the majority of

patients are on fruquintinib treatment [predicted median of [redacted] months estimated from time to treatment discontinuation (TTD) in the model]. The hazards over time for trifluridine-tipiracil are initially high, but then drop, crossing the hazards of regorafenib and fruquintinib at ~3 and 6 months, respectively. This would imply that the probability of experiencing a PFS event would be lower for trifluridine-tipiracil than fruquintinib or regorafenib from these timepoints onwards. The Company have sought additional clinical expert feedback on the plausibility of the modelled hazards over time, which advised that this trend in hazards beyond the treatment period is clinically implausible, and the risk of a PFS event following treatment with fruquintinib would be expected to be lower than that of all comparators (23). Clinicians also noted that fruquintinib may be associated with increased tumour shrinkage vs regorafenib and trifluridine-tipiracil quoting a difference of "2–5% compared with 1–1.6%", which results in longer time taken for the tumour to regrow to a volume at which it will result in a deterioration in survival outcomes (23).

The -2, -2 model results in the BSC hazards crossing the regorafenib hazards at approximately 10 months, suggesting that the risk of a PFS event following regorafenib is higher than with BSC. This is not considered to be clinically plausible, and is not supported by the observed benefit of regorafenib vs BSC in the CORRECT and CONCUR trials, as explored in TA866 (24).

As the crossing of the long-term trifluridine-tipiracil and fruquintinib hazards over time was slightly less prominent in the -3, -3 model vs other models, and this model did not predict implausible crossing of the regorafenib and BSC hazards as in the -2, -2 model, it was considered to predict the most plausible projections of hazards out of the models explored. However, there remain limitations in the plausibility of predicted hazards given the implausible crossing of the trifluridine-tipiracil and fruquintinib hazards.

Predictive accuracy of models

For the purpose of assessing the predictive accuracy of the best fitting models for PFS, the hazards estimated from the FP NMA were converted to probabilities in the model and the resulting survival curves are presented in Figure 6, Figure 7 and Figure 8. The raw survival curve output from the FP NMA (i.e. without applying to a reference curve) was then compared with the KM data from the relevant clinical trials that were used to inform the analysis.

This assessment is limited by the lack of pooled KM data for all the relevant trials informing the FP NMA for each treatment. For example, while pooled KM data for trifluridine-tipiracil are available for RECOURSE and Yoshino, and TERRA separately, the pooled KM data including all three trials are not available. Therefore, it is difficult to make conclusions with respect to predictive accuracy.

For fruquintinib, all FP models predict the pooled FRESCO and FRESCO-2 KM data well initially (in the first 6 months) whilst underpredicting the Xu KM data slightly. Towards the tail of the curve, all FP models appear to overpredict fruquintinib PFS compared with the observed data. For regorafenib, all FP models provided a relatively good fit to the observed KM data from CORRECT and CONCUR, with the estimates lying between the two KM curves. For trifluridine-tipiracil, all FP models overpredict the observed KM data from the pooled RECOURSE and Yoshino, and TERRA studies particularly towards the tail of the curves. For BSC, the FP models initially underpredict the pooled FRESCO and FRESCO-2 KM data, and then overpredict the observed KM data from ~2 months.

In all models, there is crossing observed between the fruquintinib and trifluridine-tipiracil curves, as per the hazard plots, with this being most apparent in the -3, -2 and -2, -2 models. Notably, when the -2, -2 FP model is used for PFS, the resultant regorafenib PFS curve also crosses BSC. As noted previously, this is considered to be implausible given data from the relevant RCTs and clinical opinion to the company that fruquintinib may be associated with slower deterioration of QoL and performance status (23).

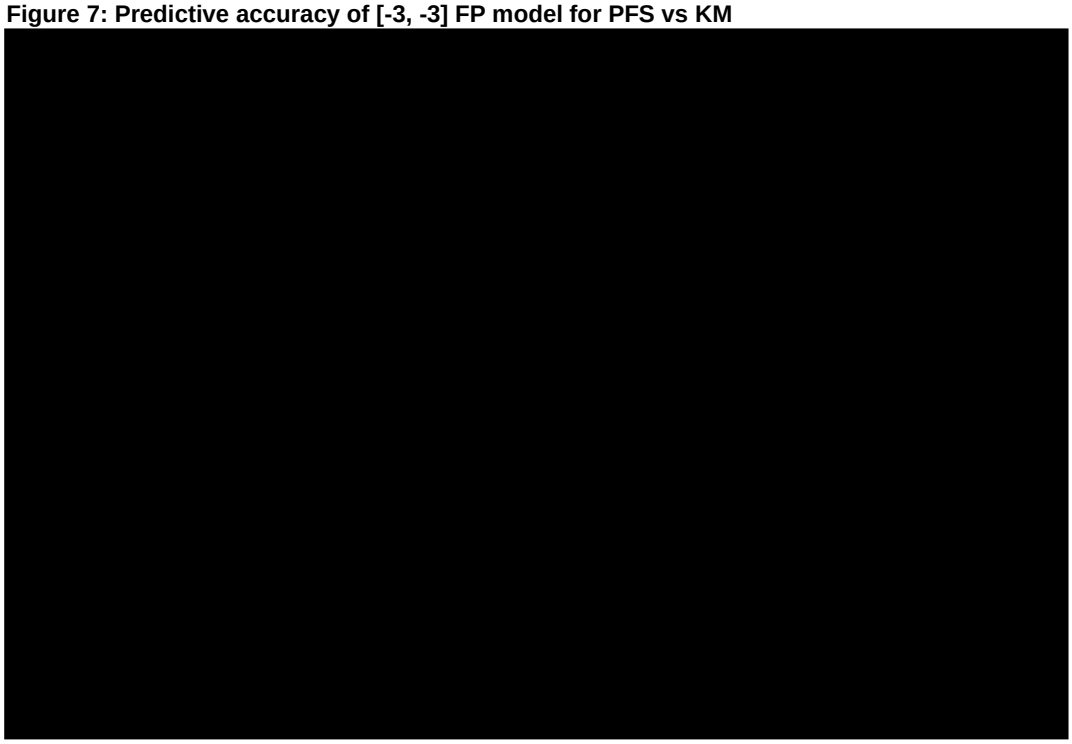
Company response to the Committee's requests following ACM2

Given the difficulties in assessing predictive accuracy due to the limitations of available pooled KM data, all models are considered to provide a similar prediction of outcomes vs the KM data.

Figure 6: Predictive accuracy of [-3, -2] FP model for PFS vs KM

Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

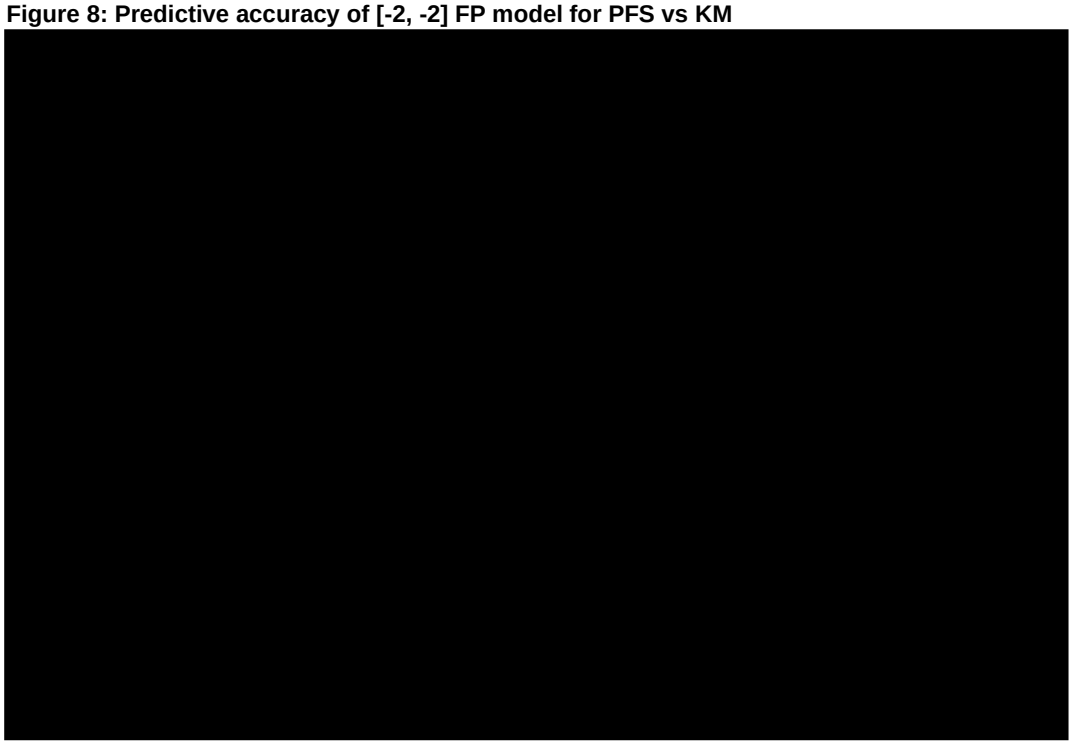
Figure 7: Predictive accuracy of [-3, -3] FP model for PFS vs KM



Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Company response to the Committee's requests following ACM2

Figure 8: Predictive accuracy of [-2, -2] FP model for PFS vs KM



Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Face validity and clinical plausibility of modelled outcomes

Hazards over time were calculated in the CEM by parameterising the output of the FP NMA, using the Beta coefficients (reported in Appendix C). HRs were then estimated and applied to the relevant reference curve in the CEM determined by the NICE Committee, as discussed in Request 1 and Request 7:

- 3L+: time-varying HRs were estimated vs trifluridine-tipiracil and applied to the relevant reference curve in the model (digitised pooled RECOURSE and Yoshino data for PFS).
- 4L+: scenario analyses are presented where (a) time-varying HRs were estimated vs regorafenib and applied to the digitised CORRECT reference curve, and (b) where FRESCO-2 is used as the reference curve (see response to Request 7).

The resulting predicted PFS curves for each treatment were used to assess face validity and clinical plausibility of modelled outcomes. The predicted HRs are presented in Appendix C.

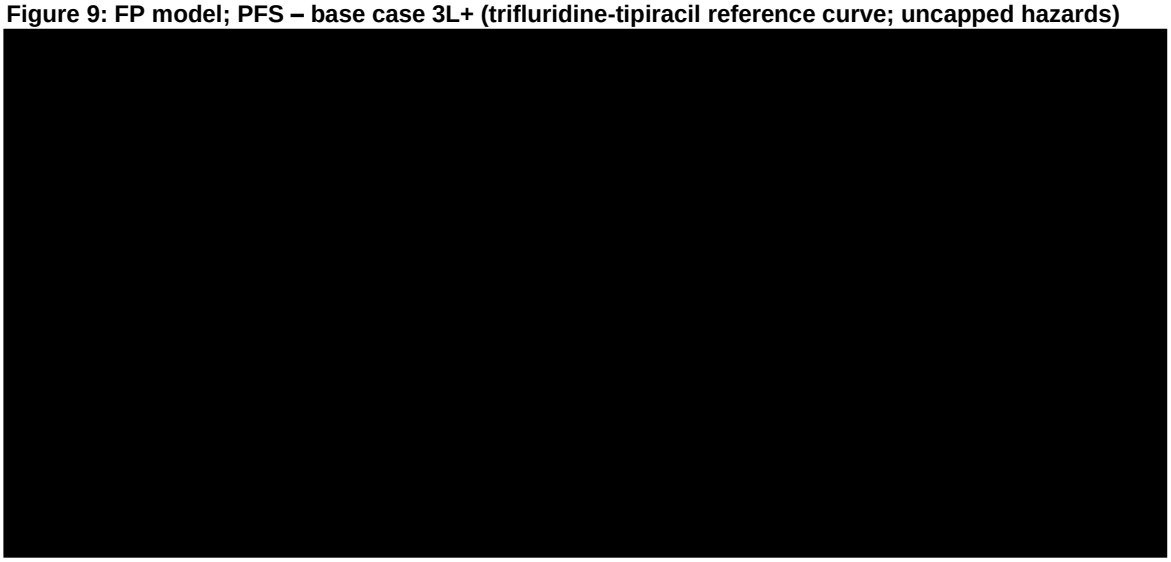
Based on the previous steps in the assessment of model selection, the -3,-3 model was considered to predict the most plausible hazards over time and survival projections out of the models explored. The -3,-3 model will therefore be the focus of the assessment of face validity and clinical plausibility of modelled outcomes. Predicted outcomes for the -3,-2 and -2,-2 models are discussed below, however associated plots and data are presented in Appendix C.

3L+ base case (trifluridine-tipiracil reference curve; pooled RECOURSE and Yoshino)

The estimated survival curves are presented in Figure 9 for the -3, -3 FP model.

Company response to the Committee's requests following ACM2

Figure 9: FP model; PFS – base case 3L+ (trifluridine-tipiracil reference curve; uncapped hazards)



Abbreviations: 3L+, third-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median PFS estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and real-world evidence (RWE), as reported in Table 4. Note that, as with the constant HR NMA, the FP NMA included a number of RCTs that have not been captured in the reference curves of the model (e.g. the TERRA study for trifluridine-tipiracil), therefore after applying the HRs from the FP NMA, it may be expected that the resultant curves would result in under- or overpredictions of the trial medians for each comparator (25). Despite this, some general alignment across source is still expected. Median estimates and landmark statistics have been used to support the overall clinical plausibility of each curve selection, when the time-varying HRs are applied to a baseline curve.

The predicted fruquintinib curve underestimates PFS compared with key clinical trials. The predicted median PFS for fruquintinib ([redacted] months), is lower than the median PFS observed in the FRESCO (3.7 months), FRESCO-2 (3.7 months) and Xu (4.7 months) studies (26-28). For regorafenib, the predicted median PFS ([redacted] months) is considered to overestimate median PFS observed in the CORRECT trial (1.9 months) but align more closely with the CONCUR (3.2 months) data and the RWE for regorafenib (2.7–3.1 months) (29-32). Therefore, the clinical benefit of fruquintinib in the PFS state may be underestimated compared with regorafenib using the FP approach.

For trifluridine-tipiracil, the predicted median PFS ([redacted] months) overestimates the medians from the pooled RECOURSE and Yoshino (1.9 months) and TERRA (2.0 months) trials, but is generally aligned when considering the median from SUNLIGHT (2.4 months), TA405 (2.9 months) and the RWE (3.2–3.3 months) (3, 25, 33-37).

Landmark estimates of survival at 6-months, 1-year and 2-years were also compared with observed data and previous TAs (Table 5):

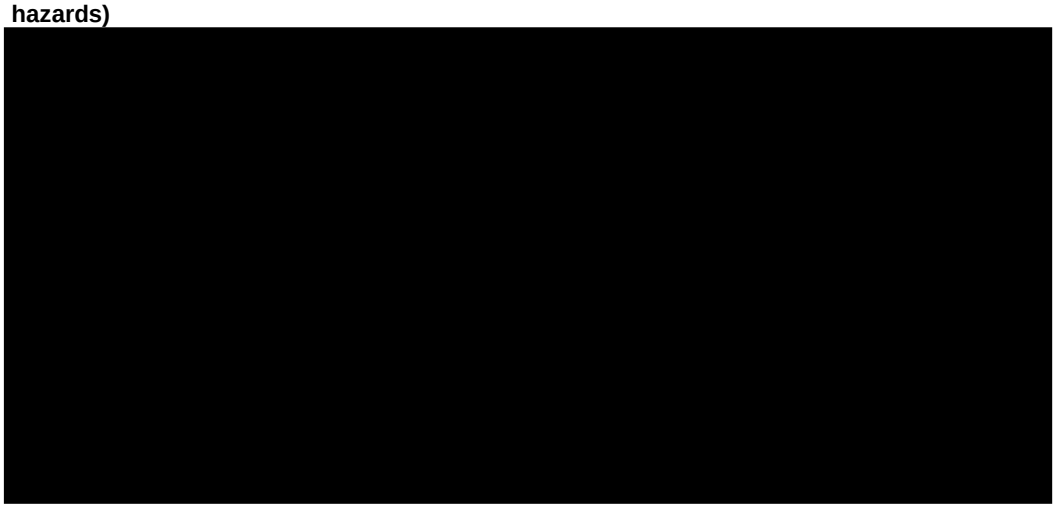
- The fruquintinib curve underpredicts the observed data with predictions of 6-month, 1-year and 2-year PFS of [redacted]%, [redacted]% and [redacted]% respectively in the 3L+ base case, compared with 25% at 6-months and 5% at 1-year in the pooled FRESCO and FRESCO-2 KM data (11)
    - 2-year PFS aligns with clinical opinion that 0% of patients would be progression-free at 2-years.
- The regorafenib curve also underpredicts the observed data with predictions of 6-month, 1-year and 2-year PFS of 9.9%, 0.8% and 0.0% compared with 4.7% at 1-year in the pooled CORRECT and CONCUR KM data (5).

Company response to the Committee's requests following ACM2

	○ The regorafenib curve also underpredicts the PFS predicted in TA866 ([redacted]% and 1.5% at 6-months and 1-year, respectively) • Trifluridine-tipiracil underpredicts the RECOURSE KM data at 6-months ([redacted]% vs 25% respectively) and 1-year ([redacted]% vs 8% respectively) (33) The median PFS estimates using the -3, -2 and -2, -2 FP models are presented in Appendix C across the 3L+ and 4L+ scenarios. For both PFS and OS, the fruquintinib curves cross with the regorafenib and trifluridine-tipiracil curves. This is not considered clinically plausible given clinical opinion to the Company which stated that the greater tumour shrinkage, quoting a difference of "2–2.5% for fruquintinib compared with trifluridine-tipiracil 1-1.6%", would result in slower deterioration in QoL and performance status and hence longer PFS (19). The implausible crossing of hazards is also the case, and to a greater extent, in the other models presented in Appendix C. Implausible crossing of curves estimated using the FP NMA approach have been reported in TA544 (Dabrafenib in combination with trametinib for V600+ malignant melanoma), TA946 (Olaparib with bevacizumab for ovarian, fallopian tube and peritoneal cancer) and TA858 (lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma) where it was similarly concluded that models did not capture the expected sustained treatment effect of the intervention vs the comparator (38-40). The associated NICE Committee in both TA544 and TA946 accepted that a continued separation of the curves was plausible, as per clinical opinion, and therefore accepted that the FP NMA predictions were implausible (41, 42). Other NICE TAs have also commented on the limitations of FP NMA predictions. For example, in TA858, fractional polynomial models were used: the results from the Company's FP NMA were considered to be highly uncertain and difficult to interpret. The final appraisal document states that "the EAG prefers a proportional hazards network meta-analysis despite uncertainty about whether the proportional hazards assumption holds", the Committee subsequently concluded that "both approaches are associated with uncertainty, but the results of the EAG's proportional hazards NMAs could be used for decision making" (40). Considering the implausible crossing of hazards over time, a scenario has therefore been explored where hazards have been capped at the point of crossing (set equal to the reference curve at 6 months i.e. HR of 1 from this time point) to model more clinically plausible outcomes (Figure 10). For PFS, the outcomes for uncapped and capped hazards are similar, and previously presented medians and landmark outcomes are unchanged. However, as crossing hazards is considered clinically implausible, the curves including capping are considered more appropriate. This also aligns with the methods used for OS. As clinical opinion to the company suggested a potential longer PFS for fruquintinib compared with regorafenib and trifluridine-tipiracil, this scenario is considered to be conservative. Capping of the hazards was employed by the Company for OS as part of NICE TA739 (atezolizumab for metastatic urothelial bladder cancer) which also utilised a FP NMA that resulted in clinically implausible values of landmark OS (43). The EAG noted the issue with the outputs of the FP NMA and raised questions around the appropriateness of using the FP NMA at all. The output of the FP NMA was also considered implausible for PFS and could not be used. A cap of the hazards was also included in the base case analysis for NICE TA724 (nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small cell lung cancer) to ensure that long-term HRs did not result in clinically implausible curves (44). While the cap is considered a conservative assumption, based on use in prior appraisals, it is considered an appropriate approach to address the limitation in predicted outcomes by the FP NMA.

Company response to the Committee's requests following ACM2

Figure 10: FP model; PFS – 3L+ base case (pooled RECOURSE/Yoshino reference curve; capped hazards)

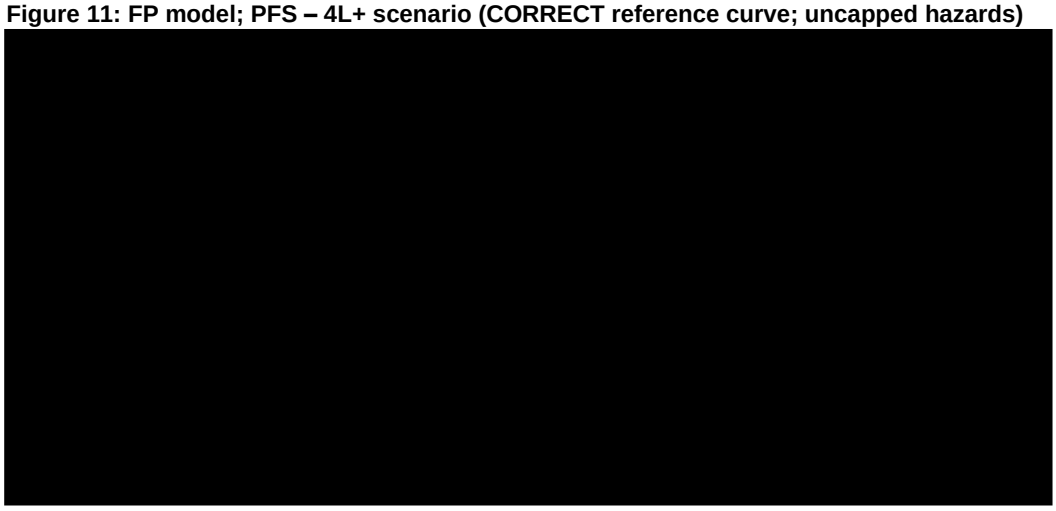


Abbreviations: 3L+, third-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

4L+ scenario (regorafenib reference curve; CORRECT data)

The estimated survival curves are presented in Figure 11 for the -3, -3 FP model. The corresponding curves for the -3, -2 and -2, -2 FP models are provided in Appendix C

Figure 11: FP model; PFS – 4L+ scenario (CORRECT reference curve; uncapped hazards)



Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median PFS estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and RWE, as reported in Table 4.

The predicted fruquintinib curve underestimates PFS compared with key clinical trials. The predicted median PFS for fruquintinib ([redacted] months), is lower than the median PFS observed in the FRESCO (3.7 months), FRESCO-2 (3.7 months) and Xu (4.7 months) studies (26-28). For regorafenib, the predicted median PFS ([redacted] months) overestimates median PFS observed in the CORRECT trial (1.9 months) but aligns more closely with the CONCUR (3.2 months) data and the RWE for regorafenib (2.7 months) (29-32). Therefore, the clinical benefit of fruquintinib in the PFS state may be underestimated compared with regorafenib using the FP approach.

For BSC, the predicted median ([redacted] months) is generally aligned with the relevant trial data (1.8 months in the pooled FRESCO and FRESCO-2 data and 1.0 month in Xu) (11, 28).

Company response to the Committee's requests following ACM2

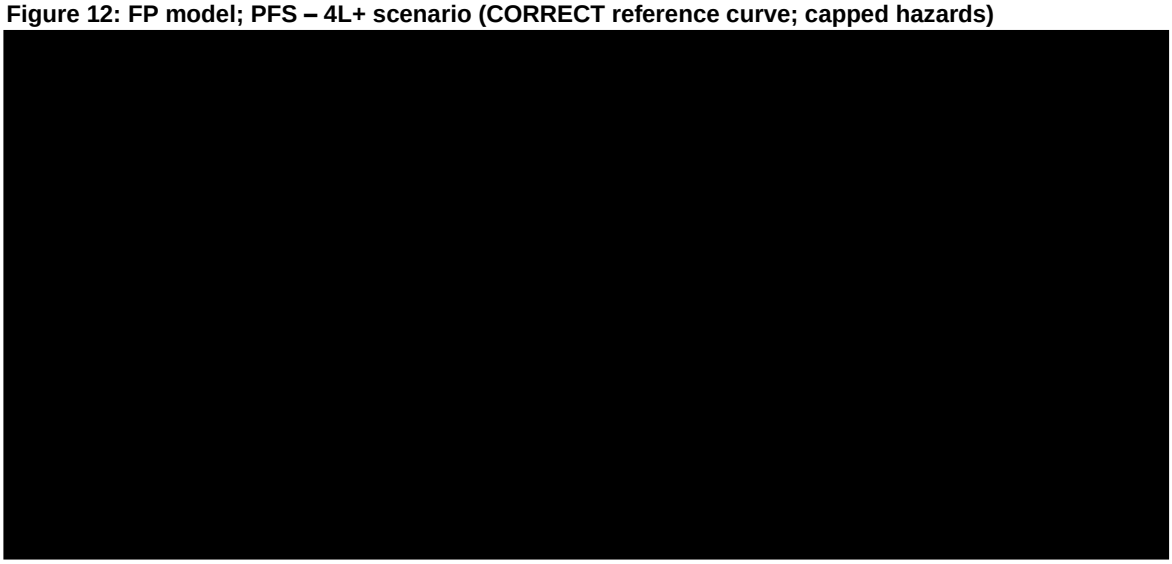
Landmark estimates of survival at 6-months, 1-year and 2-years were also compared with observed data and previous TAs (Table 5):

- The fruquintinib curve better predicts the observed data in the 4L+ scenario with predictions of 6-month, 1-year and 2-year PFS of [redacted]%, [redacted]% and [redacted]% respectively when using the CORRECT curve as the reference, compared with 25% at 6-months and 5% at 1-year in the pooled FRESCO and FRESCO-2 KM data (11, 29)
    - However, 2-year PFS overpredicts clinical opinion that 0% of patients would be progression-free at 2-years.
- Predictions of landmark PFS for BSC (6-month, 1-year and 2-year PFS of [redacted]%, [redacted]% and [redacted]%) generally align with the trial data (1.7% and 0% at 6-months and 1-year in the pooled FRESCO and FRESCO-2 data), predictions from previous TA's (2.1% and 0.2% at 6-months and 1-year in the pooled CORRECT and CONCUR data) and clinical opinion that 0% of patients would be progression-free at 2-years (5, 11)

Median PFS estimates using the -3, -2 and -2, -2 FP models are presented in the Appendix for the 3L+ and 4L+ scenarios.

As with other scenarios, the fruquintinib curves cross with the regorafenib and trifluridine-tipiracil curves. Therefore, the fruquintinib hazards have been capped (set equal to the reference curve at the point of crossing) to model more clinically plausible outcomes (Figure 12). For PFS, the outcomes for uncapped and capped hazards are similar, and previously presented medians and landmark outcomes are unchanged. However, as crossing hazards is considered clinically implausible, the curves including capping are considered more appropriate, and this also aligns with the methods used for OS.

Figure 12: FP model; PFS – 4L+ scenario (CORRECT reference curve; capped hazards)



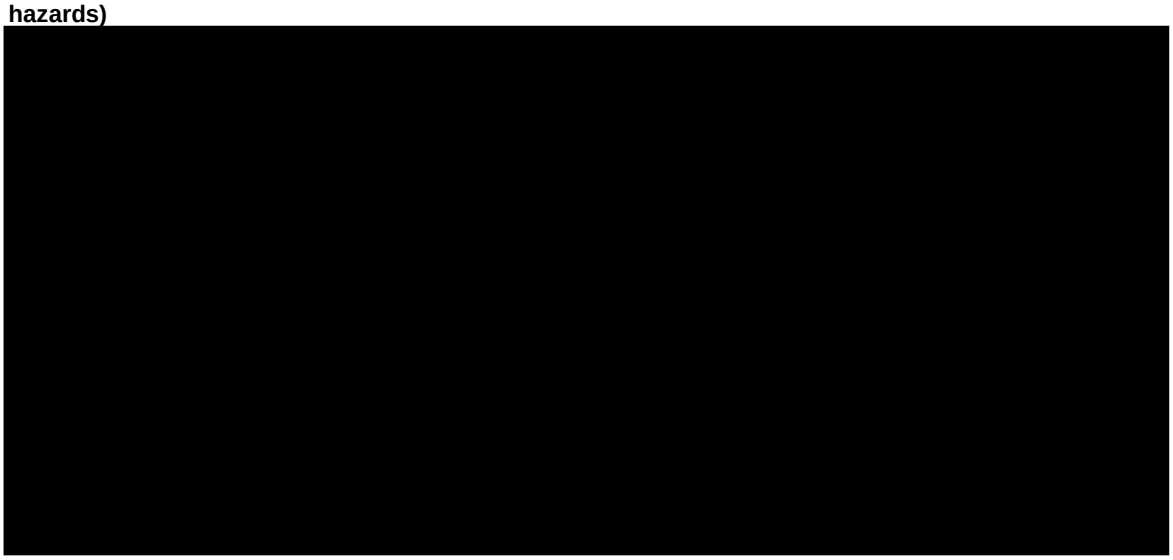
Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

4L+ scenario (fruquintinib reference curve; FRESCO-2 data)

The estimated survival curves are presented in Figure 13 for the -3, -3 FP model. The corresponding curves for the -3, -2 and -2, -2 FP models are provided in Appendix C.

Company response to the Committee's requests following ACM2

Figure 13: FP model vs observed data; PFS – 4L+ scenario (FRESCO-2 reference curve; uncapped hazards)



Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median PFS estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and RWE, as reported in Table 4.

The predicted curve underestimates fruquintinib outcomes compared with key clinical trials. The median PFS for fruquintinib ([redacted] months), is lower than the median PFS observed in the FRESCO (3.7 months), FRESCO-2 (3.7 months) and Xu (4.7 months) studies (26-28). For regorafenib, the predicted median PFS ([redacted] months) overestimates median PFS observed in the CORRECT trial (1.9 months) but aligns more closely with the CONCUR (3.2 months) data and the RWE for regorafenib (2.7-3.1 months) (29-32). Therefore, the clinical benefit of fruquintinib in the PFS state may be underestimated compared with regorafenib using the FP approach.

For BSC, the predicted median ([redacted] months) is generally aligned with the relevant trial data (1.8 months in the pooled FRESCO and FRESCO-2 data and 1.0 month in Xu) (11, 28).

Landmark estimates of survival at 6-months, 1-year and 2-years were also compared with observed data and previous TAs (Table 5):

- The fruquintinib curve better predicts the pooled FRESCO and FRESCO-2 KM data (25% at 6-months and 5% at 1-year) in the 4L+ scenarios with 6-month, 1-year and 2-year PFS of [redacted]%, [redacted]% and [redacted]% when using the FRESCO-2 curve as the reference curve (11)
    - 2-year PFS aligns with clinical opinion that 0% of patients would be progression-free at 2-years.
- The predictions of PFS for regorafenib are similar at 6-months when the CORRECT reference curve is used ([redacted]%) and when the FRESCO-2 reference curve is used ([redacted]%) (27, 29)
- Predictions of landmark PFS for BSC (6-month, 1-year and 2-year PFS of [redacted]%, [redacted]% and [redacted]%) generally align with the trial data (1.7% and 0% at 6-months and 1-year in the pooled FRESCO and FRESCO-2 data), predictions from previous TA's (2.1% and 0.2% at 6-months and 1-year in the pooled CORRECT and CONCUR data) and clinical opinion that 0% of patients would be progression-free at 2-years (5, 11)

The median PFS estimated using the -3, -2 and -2, -2 FP models is presented in Appendix C across the 3L+ and 4L+ scenarios.

Company response to the Committee's requests following ACM2

As with other scenarios, the fruquintinib curves cross with the regorafenib and trifluridine-tipiracil curves. A scenario has therefore been explored where hazards have been capped to model more clinically plausible outcomes (Figure 14). For the scenario where FRESCO-2 is used as the reference curve in the 4L+ population, the capping is applied instead to the regorafenib hazards. This is considered to be equivalent methodologically to the capping applied in the 3L+ and 4L+ (CORRECT reference curve) scenarios. For PFS, the outcomes for uncapped and capped hazards are similar, and previously presented medians and landmark outcomes are unchanged. However, as crossing hazards is considered clinically implausible, the curves including capping are considered more appropriate, and this also aligns with the methods used for OS.

Figure 14: FP model vs observed data; PFS – 4L+ scenario (FRESCO-2 reference curve; capped hazards)

Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Takeda consider that the outcomes when using FRESCO-2 as the reference curve are more appropriate, as they more closely align with the FRESCO and FRESCO-2 trial data for fruquintinib and are more closely aligned with clinical opinion that 0% of patients would be progression-free at 2-years (26, 27). Furthermore, when CORRECT is used as the reference curve, the model produces estimates of 2-year PFS that are better than the 3L+ base case, for both fruquintinib ([redacted]% vs [redacted]%) and regorafenib ([redacted]% for [redacted]%) (29). This is not considered to have face validity given that outcomes generally worsen with each additional line of therapy.

Table 4: Comparison of PFS outcomes

Approach	Median PFS, months
Fruquintinib	
FRESCO (26)	3.7
FRESCO-2 (27)	3.7
Xu, 2012 (28)	4.7
Pooled FRESCO and FRESCO data (11)	3.7
Without capping of hazards	
3L+ Base Case (-3,-3 FP NMA applied to pooled RECOURSE and Yoshino curve)	[redacted]
4L+ scenario analysis A (-3,-3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3,-3 FP NMA applied to FRESCO-2 reference curve)	[redacted]
With capping of hazards	
3L+ Base Case (-3,-3 FP NMA applied to pooled RECOURSE and Yoshino curve)	[redacted]

Company response to the Committee's requests following ACM2

4L+ scenario analysis A (-3,-3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3,-3 FP NMA applied to FRESCO-2 reference curve)	[redacted]
Regorafenib	
CORRECT (29)	1.9
CONCUR (30)	3.2
TA866 model predicted value (5)	2.8
Pooled CORRECT and CONCUR (5, 29, 30)	2.1
REBECCA RWE study (31)	2.7
CORRELATE RWE study (45)	2.9
RECORA RWE study (32)	3.1
3L+ Base Case (-3,-3 FP NMA applied to pooled RECOURSE and Yoshino curve)	[redacted]
4L+ scenario analysis A (-3,-3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3,-3 FP NMA applied to FRESCO-2 reference curve)	[redacted]
Trifluridine-tipiracil	
RECOURSE (33)	2.0
TERRA (25)	2.0
Yoshino (34)	2.0
TA405 model predicted value (3)	2.9
Pooled RECOURSE and Yoshino (3)	1.9
Trifluridine-tipiracil monotherapy reported in SUNLIGHT (46) (6)	2.4
Tong 2021 RWE study (36)	3.2
Stavraka 2021 RWE study (37)	3.3
3L+ Base Case (-3,-3 FP NMA applied to pooled RECOURSE and Yoshino curve)	[redacted]
BSC	
FRESCO (26)	1.8
FRESCO-2 (27)	1.8
Xu, 2012 (28)	1.0
Pooled FRESCO and FRESCO data (11)	1.8
CORRECT (29)	1.7
CONCUR (30)	1.7
Pooled CORRECT and CONCUR (5, 29, 30)	1.8
TA405 model predicted value (3)	1.6
RECOURSE (33)	1.7
TERRA (25)	1.8
Yoshino (34)	1.0
Pooled RECOURSE and Yoshino (3)	1.7
4L+ scenario analysis A (-3,-3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3,-3 FP NMA applied to FRESCO-2 reference curve)	[redacted]

Abbreviations: BSC, best supportive care; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence.

Company response to the Committee's requests following ACM2

Table 5: Comparison of PFS outcomes; landmark stats

Approach	6 month PFS	1-year PFS	2-year PFS
Fruquintinib			
Constant HR NMA	[redacted]	[redacted]	[redacted]
Clinical opinion	-	-	0%
Pooled FRESCO and FRESCO-2 data (11)	25%	5%	-
Without capping of the hazards			
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil pooled RECOURSE/Yoshino curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]	[redacted]	[redacted]
With capping of the hazards			
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil pooled RECOURSE/Yoshino curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]	[redacted]	[redacted]
Regorafenib			
Constant HR NMA	[redacted]	[redacted]	[redacted]
TA866 model predicted value (5)	12.1%	1.5%	-
Pooled CORRECT and CONCUR (5, 29, 30)	-	4.7%	-
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil			
RECOURSE (33)	25%	8%	-
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]	[redacted]	[redacted]
BSC			
FRESCO-2 (27)	1.1%	-	-
Pooled FRESCO and FRESCO data (11)	1.7%	0%	0%
Pooled CONCUR and CORRECT	2.1%	0.2%	-
Clinical opinion	-	-	0%

4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RWE, real-world evidence.

Overall survival

Statistical goodness of fit

The DIC statistics for the nine first-order and 54 second-order models, along with model convergence as described previously, were explored. The top fitting models are presented in Table 6 for OS. DIC statistics for all FE and RE models are reported in Appendix C, Table 23 and Table 24, respectively.

Table 6: Top Fitting Models - OS

P1	P2	Dbar	Dhat	pD	FE_DIC	FE_rank	Dbar	Dhat	pD	RE_DIC	RE_rank
-3	-3	1133	1100	32.38	1165	1	1131	1095	35.49	1166	1
-3	-2	1133	1101	32.28	1165	1	1131	1095	35.69	1166	2
-2	-2	1135	1102	32.38	1167	2	1133	1097	35.92	1169	3

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effects; OS, overall survival; P1, 1st Power; P2, 2nd Power; pD, leverage (effective number of parameters); RCT, randomised controlled trial; RE, random-effects.

The top fitting models by DIC are aligned between OS and PFS, as well as the FE and RE rankings. For both FE and RE analyses, functions of time that included 1/time^3 (-3,-3) offered the best fit.

These three models that provided the best statistical fit based on DIC were considered in further model selection assessments: this was considered a pragmatic approach given time restraints on conducting these analyses. This also aligns with the approach that was taken in TA997 (pembrolizumab with chemotherapy in adenocarcinoma) which was considered acceptable by NICE (22).

Face validity of hazards over time

The FE and RE provided similar DIC statistics for each model (within three points), and the hazards over time were comparable across models. As RE models are associated with challenges regarding the convergence for PFS models and lack of statistical heterogeneity in PFS found between trials in the direct meta-analysis, and in general, parsimonious models are preferred, the FE models were considered for further model fit assessments. This was considered reasonable given the time limitations on completing these analyses. Plots of hazards over time for the RE models are presented in Appendix C.

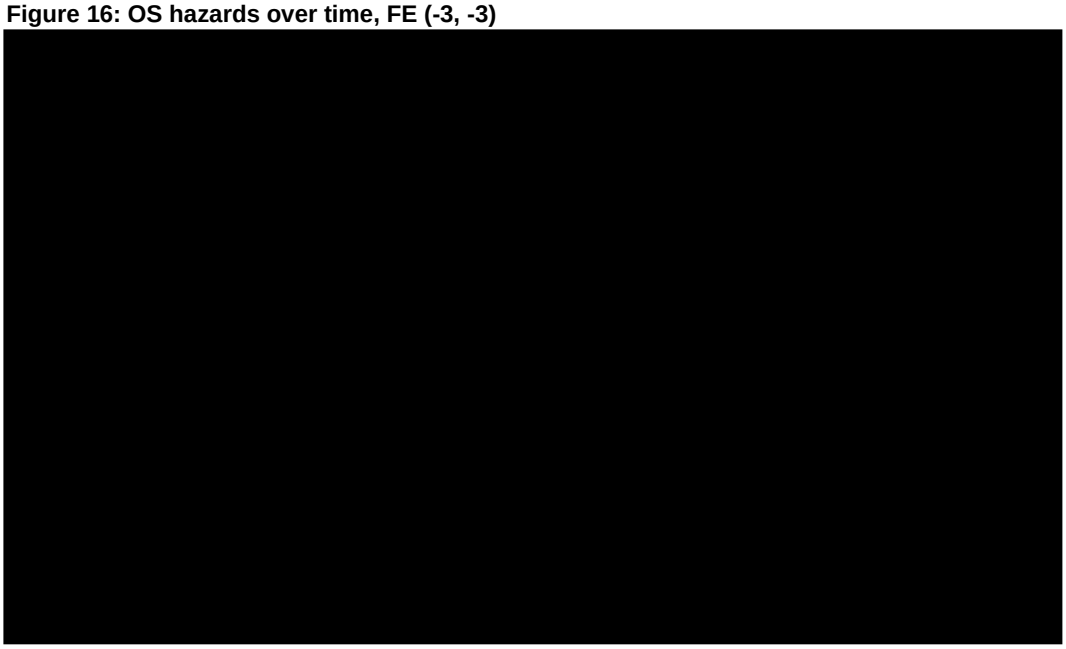
For the best-fitting FE FP NMA models for OS by DIC, hazards were estimated in the model across a lifetime time horizon, by extrapolating the respective beta coefficients (presented in Appendix C). The face validity of predicted hazards over time was assessed. Plots of hazards over time for the (-3, -2), (-3, -3) and (-2,-2) models are presented in Figure 15, Figure 16, and Figure 17, respectively.

Company response to the Committee's requests following ACM2

Figure 15: OS hazards over time, FE (-3, -2)

Abbreviations: BSC, best supportive care; FE, fixed effects; Fruq, fruquintinib; OS, overall survival.

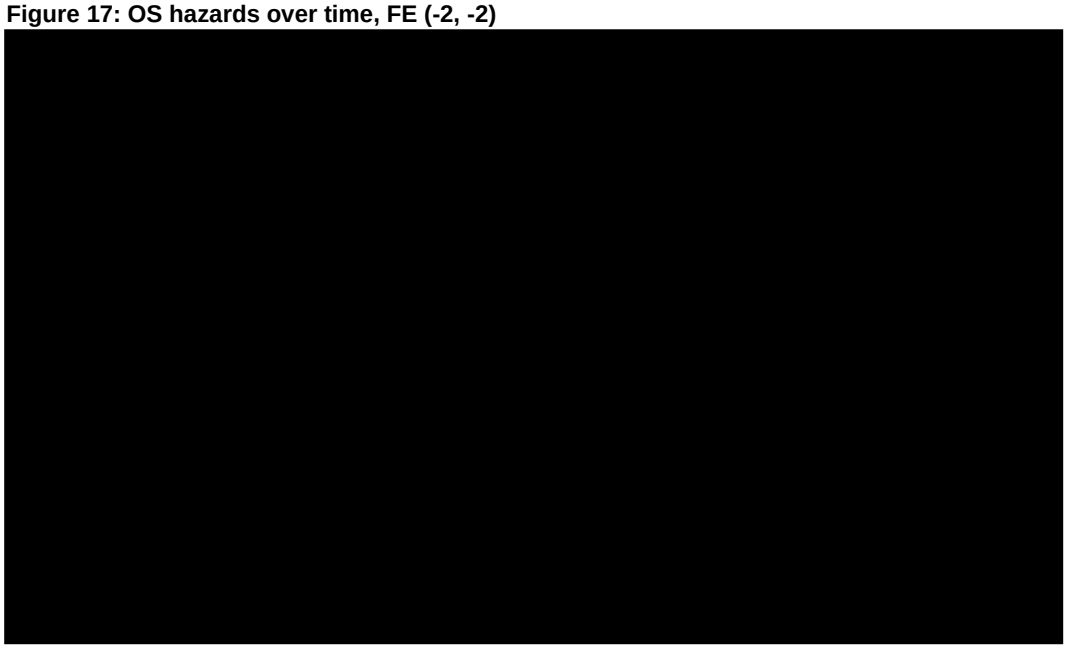
Figure 16: OS hazards over time, FE (-3, -3)



Abbreviations: BSC, best supportive care; FE, fixed effects; Fruq, fruquintinib; OS, overall survival.

Company response to the Committee's requests following ACM2

Figure 17: OS hazards over time, FE (-2, -2)



Abbreviations: BSC, best supportive care; FE, fixed effects; Fruq, fruquintinib; OS, overall survival.

On visual inspection of the hazards over time, the shape of the hazards for each treatment is similar across all explored models. In all models, fruquintinib demonstrates favourable OS hazards vs all comparators in the initial period of up to ~4.5 months, considered to reflect the time that most patients will be on treatment [predicted median of 2.76 months estimated from TTD in the model]. The regorafenib and trifluridine-tipiracil hazards are comparable over time. At ~4.5 months, the OS hazards for fruquintinib cross with those of active comparators, implying that the probability of dying would be greater with fruquintinib from these points onwards vs regorafenib and trifluridine-tipiracil. The Company have sought additional clinical expert feedback on the plausibility of the modelled hazards over time, which has advised that this trend in hazards beyond the treatment period is clinically implausible, and the risk of death following treatment with fruquintinib would be expected to be lower than that of all comparators (23).

Clinical experts consulted by the Company noted that fruquintinib may be associated with increased tumour shrinkage vs regorafenib and trifluridine-tipiracil, quoting a difference of "2–5% compared with 1–1.6%", which would result in sustained OS benefit. This is also the case for DCR rates, which are higher in the fruquintinib arm [62.2% and 55.5% in FRESCO and FRESCO-2 respectively (Table 13 of Document B)] compared with trifluridine-tipiracil (44% in the RECOURSE trial) and regorafenib (30.3% in the CORRECT trial) and result in the disease taking longer to grow to a "fatal volume" (5, 23, 47). Therefore, the OS hazard for fruquintinib would be expected to remain below those of active comparators (vs placebo), or at a minimum, be the same as the active comparators. Furthermore, given that clinical experts added that improved PFS can be expected to translate to improved OS, and the PFS hazards for fruquintinib remain consistently below those of regorafenib for the majority of the follow-up period, the crossing of the OS hazards is not clinically plausible (23).

The -3, -2 and -2, -2 FP NMA models predict that the hazards for fruquintinib exceed that of BSC over time. This is considered highly clinically implausible given the observed benefit of fruquintinib vs BSC in the FRESCO, FRESCO-2 and Xu studies, as well as the RWE and clinical expert opinion (23, 26-28). There is no biological reason why the risk of death following fruquintinib would converge with or exceed the risk of death following treatment with BSC only.

Whilst the -3, -3 FP model results in implausible hazards in terms of the crossing of the fruquintinib curve with active comparators, this is considered the most plausible of the three FP models, given that the hazards over time with fruquintinib do not exceed those with BSC.

Company response to the Committee's requests following ACM2

Predictive accuracy of models

For the purpose of assessing the predictive accuracy of the best fitting models for OS, the hazards estimated from the FP NMA were converted to probabilities in the model and the resulting survival curves are presented in Figure 18, Figure 19 and Figure 20. The raw survival curve output from the FP NMA (i.e. without applying to a reference curve) was then compared with the KM data from the relevant clinical trials that were used to inform the analysis.

Consistent with PFS, this assessment is limited by the lack of pooled KM data for all the relevant trials informing the FP NMA for each treatment. For example, while pooled KM data for trifluridine-tipiracil are available for RECOURSE and Yoshino, and TERRA separately, the pooled KM data including all 3 trials are not available (3, 25). Therefore, it is difficult to make conclusions with respect to predictive accuracy.

For fruquintinib, all FP models heavily underpredict OS compared with the pooled FRESCO and FRESCO-2, and the Xu studies (11, 28). This highlights that the crossing in the hazards observed between fruquintinib and active comparators results in highly implausible survival outputs. For regorafenib and trifluridine-tipiracil, the FP models appear to initially underpredict the KM curves from the relevant trials, however, provide a good fit to the observed data towards the tail. Therefore, the benefit of fruquintinib observed in the FRESCO and FRESCO-2 trials is not being captured by the FP models relative to data from relevant trials for regorafenib and trifluridine-tipiracil. BSC is underpredicted in all FP models compared with the relevant trial data, particularly towards the tail of the pooled FRESCO and FRESCO-2 KM curve (11).

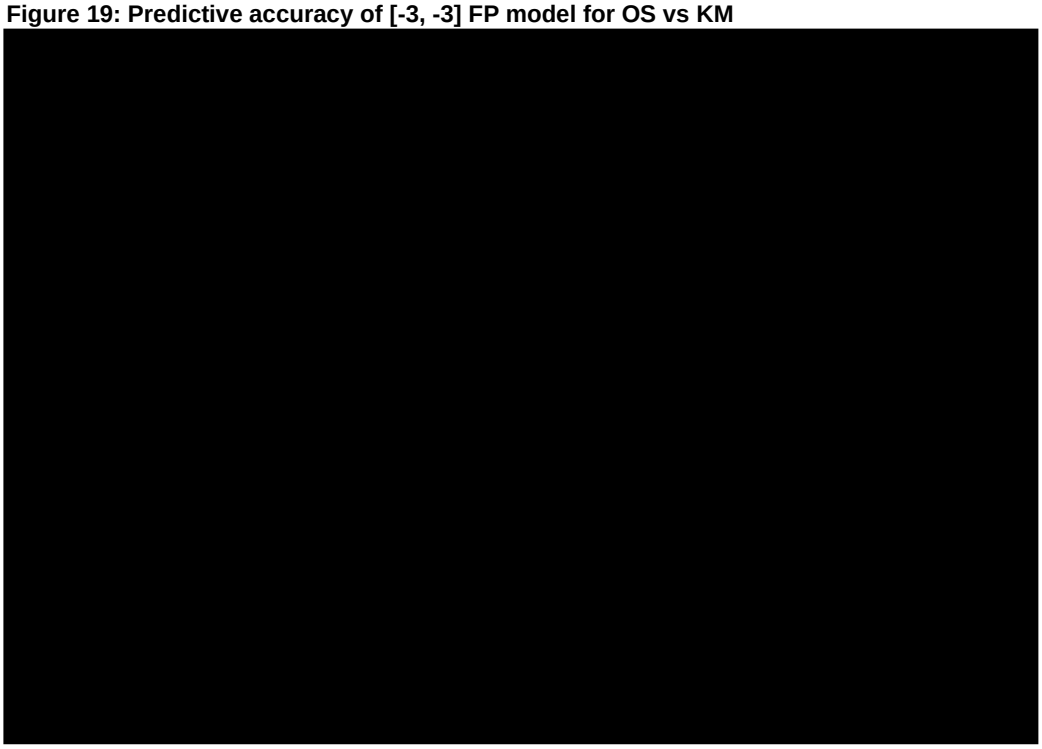
Notably, when the -2, -2 FP model is used for OS, the resultant survival curve for fruquintinib falls below the BSC curve between 6 and 12 months. Given the observed benefit of fruquintinib vs BSC in the FRESCO and FRESCO-2 studies, as well as the RWE, this is considered to be highly implausible. The -3, -3 model for fruquintinib appears to underestimate the observed data the least of the three considered models.

Figure 18: Predictive accuracy of [-3, -2] FP model for OS vs KM

Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan Meier; OS, overall survival.

Company response to the Committee's requests following ACM2

Figure 19: Predictive accuracy of [-3, -3] FP model for OS vs KM



Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan Meier; OS, overall survival.

Figure 20: Predictive accuracy of [-2, -2] FP model for OS vs KM

Abbreviations: BSC, best supportive care; FP, fractional polynomial; KM, Kaplan-Meier; OS, overall survival.

Company response to the Committee's requests following ACM2

Face validity and clinical plausibility of modelled outcomes

Hazards over time were calculated in the CEM by parameterising the output of the FP NMA, using the Beta coefficients (reported in Appendix C). HRs were then estimated and applied to the relevant reference curve in the CEM determined by the NICE Committee Request 1 and Request 7:

- 3L+: time-varying HRs were estimated vs trifluridine-tipiracil and applied to the relevant reference curve in the model (digitised SACT data for OS).
- 4L+: scenario analyses are presented where (a) time-varying HRs were estimated vs regorafenib and applied to the digitised CORRECT reference curve, and (b) where FRESCO-2 is used as the reference curve (see response to Request 7).

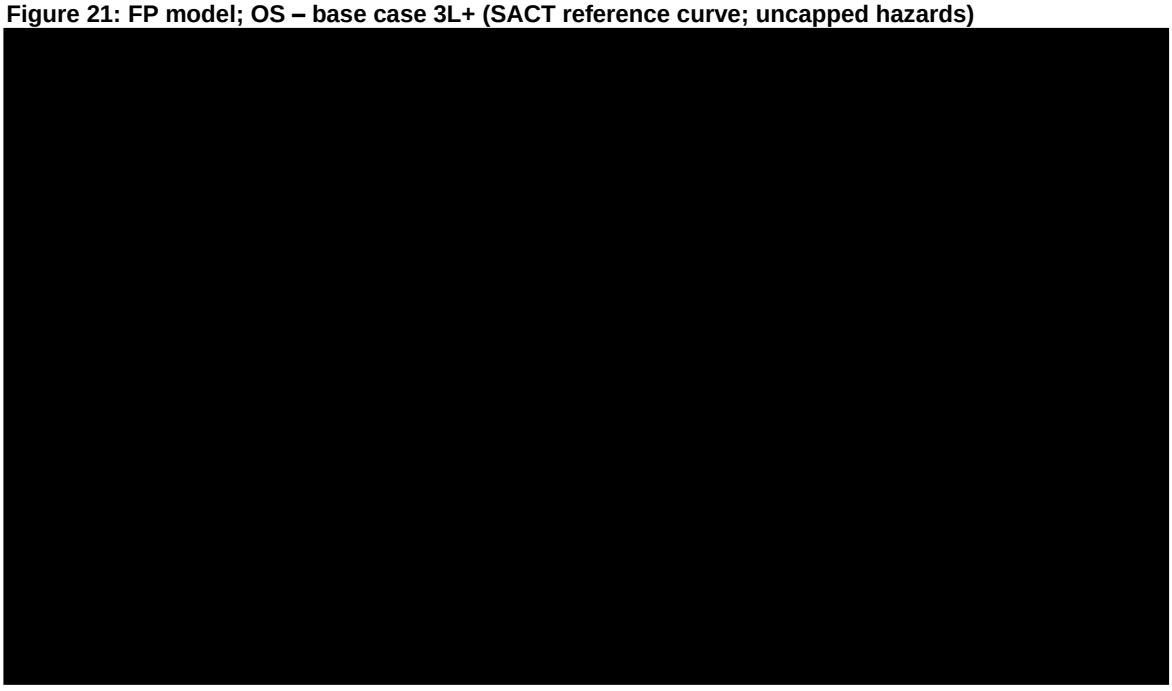
The resulting predicted OS curves for each treatment were used to assess face validity and clinical plausibility of modelled outcomes. The predicted HRs are presented in Appendix C.

Based on the previous steps in the assessment of model selection, the -3,-3 model was considered to predict the most plausible hazards over time and survival projections out of the models explored. The -3,-3 model will therefore be the focus of the assessment of face validity and clinical plausibility of modelled outcomes. Predicted outcomes for the -3,-2 and -2,-2 models are discussed below, however associated plots and data are presented in Appendix C.

3L+ base case (trifluridine-tipiracil reference curve; SACT data)

The estimated survival curves for each scenario based on the -3, -3 models are presented in Figure 21.

Figure 21: FP model; OS – base case 3L+ (SACT reference curve; uncapped hazards)



Abbreviations: 3L+, third-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and RWE in Table 7. It is important to note that, similar to the FP analysis for PFS, the FP NMA included a number of RCTs which have not been captured in the reference curves of the model (e.g. the TERRA study for trifluridine-tipiracil), therefore it would not necessarily be expected that curves should align fully to any single estimate

from the observed data (25). Median estimates have been used to support the overall clinical plausibility of each curve selection, when the time-varying HRs are applied to a baseline curve.

The median OS for fruquintinib using the FP NMA time-varying HRs ([redacted] months) underpredicts the median OS from FRESCO-2 (7.4 months), Xu (7.7 months), FRESCO (9.3 months), and the pooled FRESCO and FRESCO-2 data (8.0 months) (11, 26-28). For regorafenib, the median OS ([redacted] months) is aligned with the trial data from pooled CORRECT and CONCUR data (6.9 months) and the RWE for regorafenib (5.8–7.6 months) (5, 29-32). For trifluridine-tipiracil, the predictions of the median OS aligned with the RCTs and RWE for the 3L+ base case ([redacted] months compared with 7.3 months in the pooled RECOURSE and Yoshino trials, and 5.8–7.6 months reported in the RWE) (3, 25, 33, 34, 36, 37).

Landmark estimates of survival at 1-year, 2-years and 5-years were also compared with observed data and previous technology appraisals (Table 8):

- The fruquintinib curve underpredicts the observed data with predictions of 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]% respectively, compared with 30% in the pooled FRESCO and FRESCO-2 KM data at 1-year (11)
    - The fruquintib curve also underpredicts clinical opinion of 8–10% OS and 1% OS at 2-years and 5-years respectively, which were the values considered plausible by clinicians at the December 2023 UK market access advisory board as discussed in the Original Company Submission (Document B.3.3.2.1) (8).
    - As with PFS, the implausible crossing of hazards/survival curves that are presented in the NMA outputs also translated into implausible crossing of survival curves and therefore implausible predicted outcomes for fruquintinib. It should be noted that this is also the case, and to a greater extent, in the other FP models presented in Appendix C (-3, -2 and -2, -2).
- The regorafenib curve slightly over predicts 5-year OS with [redacted]%, compared with 0.4% predicted by the company in TA866 (5)

The median OS estimates using the -3, -2 and -2, -2 FP models are presented in Appendix C across the 3L+ base case and 4L+ scenarios.

As previously mentioned, for both PFS and OS, the fruquintinib curves cross with the regorafenib and trifluridine-tipiracil curves. This is not considered clinically plausible given clinical opinion to the Company which stated that the greater tumour shrinkage, quoting a difference of "2–2.5% for fruquintinib compared with trifluridine-tipiracil 1-1.6%", would result in slower deterioration in QoL and performance status and hence longer survival (19). The implausible crossing of hazards is also the case, and to a greater extent, in the other models presented in Appendix C.

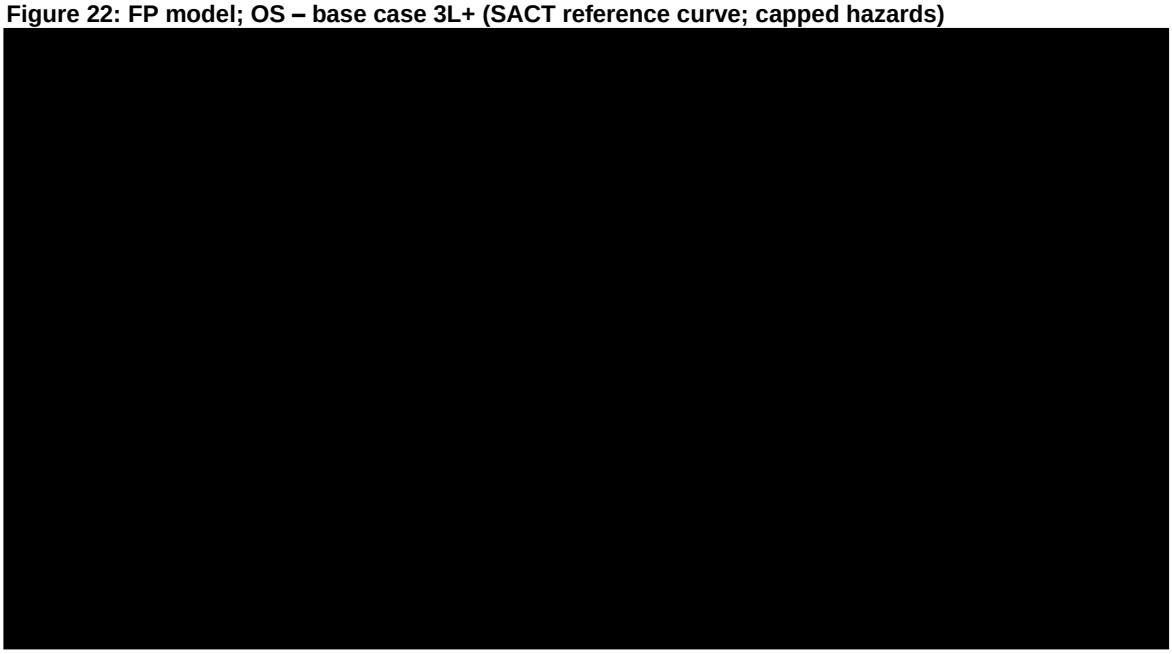
As previously discussed, implausible crossing of curves estimated using the FP NMA approach have been reported in TA544 (Dabrafenib in combination with trametinib for V600+ malignant melanoma), TA946 (Olaparib with bevacizumab for ovarian, fallopian tube and peritoneal cancer) and TA858 (lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma) based on an overview of the available clinical data where it was similarly concluded the models did not capture the expectation that the intervention was associated with a sustained treatment effect of the intervention vs the comparator (38-40). The associated NICE Committee in both TA544 and TA946 accepted that a continued separation of the curves was plausible, as per clinical opinion, and therefore accepted that the FP NMA predictions were implausible (41, 42). Other NICE TAs have also commented on the limitations of FP NMA predictions. For example, in TA858, fractional polynomial models were used: the results from the Company's FP NMA were considered to be highly uncertain, and difficult to interpret. The final appraisal document states that "the EAG prefers a proportional hazards

network meta-analysis despite uncertainty about whether the proportional hazards assumption holds", the Committee subsequently concluded that "both approaches are associated with uncertainty, but the results of the EAG's proportional hazards NMAs could be used for decision making" (40). The implausible crossing of hazards is also the case, and to a greater extent, in the other models presented in Appendix C.

Capping of the hazards was employed by the Company for OS as part of NICE TA739 (atezolizumab for metastatic urothelial bladder cancer) which also utilised a FP NMA, which resulted in clinically implausible values of landmark OS (43). The EAG noted the issue with the outputs of the FP NMA and raised questions around the appropriateness of using the FP NMA at all. The output of the FP NMA was also considered implausible for PFS and could not be used. A cap of the hazards was also included in the base case analysis for NICE TA724 (Nivolumab with ipilimumab and chemotherapy for untreated metastatic non-small cell lung cancer) to ensure that long-term HRs did not result in clinically implausible curves (44). While the cap is considered a conservative assumption, based on use in prior appraisals, it is considered an appropriate approach to address the limitation in predicted outcomes by the FP NMA.

Therefore, hazards have been capped to model more clinically plausible outcomes, as with PFS (Figure 22). The fruquintinib curve is estimated after capping the hazards at 5 months (set equal to the reference curve at the point of crossing), in line with clinical opinion to the Company, which stated that greater tumour shrinkage and DCR rates may translate to longer OS, and that PFS benefit would be expected to result in OS benefit. This is therefore considered a conservative assumption. It should be noted that when capping is applied, all FP models produce similar outcomes, and therefore the choice of model has limited impact on results (Appendix C).

Figure 22: FP model; OS – base case 3L+ (SACT reference curve; capped hazards)



Abbreviations: 3L+, third-line plus; FP, fractional polynomial; KM, Kaplan Meier; OS, overall survival.

With capping, the fruquintinib and regorafenib curves are well aligned with the trial data, and clinical opinion:

- The fruquintinib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]% respectively, compared with 30% in the pooled FRESCO and FRESCO-2 KM data at 1-year
- The fruquintinib curve aligns well with 8–10% and 1% at 2-years and 5-years respectively, which were the values considered plausible by clinicians at the December 2023 UK market

access advisory board as discussed in the Original Company Submission (Document B.3.3.2.1).

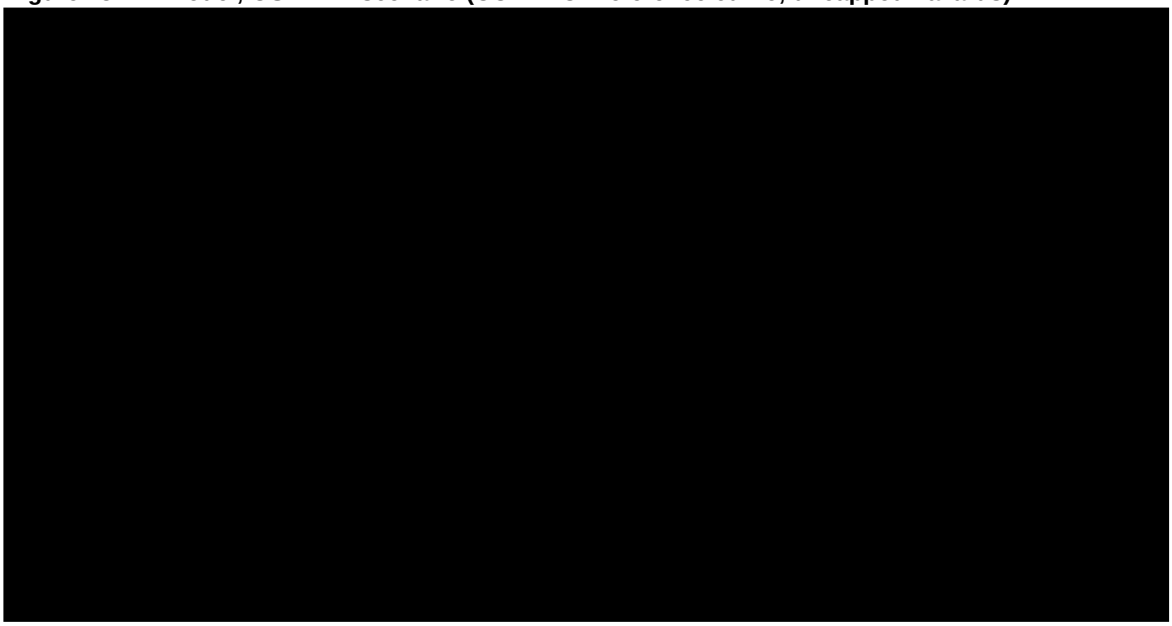
- The median OS ([redacted] months) is well aligned with FRESCO-2 (7.4 months), the pooled FRESCO and FRESCO-2 data (Median OS of 8.0 months), and Xu (Median OS of 7.7 months)

Therefore, the -3, -3 FP model overall provides a good fit to the clinical trial data when capping is applied. This further highlights the implausibility of the hazards crossing for fruquintinib and the relevant comparators. Median OS for each curve choice and curves with no capping are presented in Appendix C.

4L+ scenario (regorafenib reference curve; CORRECT data)

The predicted survival curves for each scenario based on the -3, -3 models are presented in Figure 23. The corresponding curves for the -3, -2 and -2, -2 FP models are provided in the Appendix C.

Figure 23: FP model; OS – 4L+ scenario (CORRECT reference curve; uncapped hazards)



Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and real-world evidence in Table 7.

Median OS for fruquintinib using the FP NMA time-varying HRs ([redacted] months) underpredicts the median OS from FRESCO-2 (7.4 months), Xu (7.7 months), FRESCO (9.3 months), and the pooled FRESCO and FRESCO-2 data (8.0 months). For regorafenib, the median OS ([redacted] months) is aligned with the trial data from pooled CORRECT and CONCUR data (6.9 months) and the RWE for regorafenib (5.8–7.6 months). For BSC, the predictions of the median OS using the FP NMA -3, -3 model underpredicted the RCTs slightly for the 4L+ scenario ([redacted] months) compared with a pooled FRESCO and FRESCO-2 median OS of 5.5 months).

Landmark estimates of survival at 1-year, 2-years and 5-years were also compared with observed data and previous TAs (Table 8):

Company response to the Committee's requests following ACM2

- The fruquintinib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]%, compared with 30% in the pooled FRESCO and FRESCO-2 KM data at 1-year.
    - The fruquintinib curve also underpredicts clinical opinion of 8–10% OS and 1% OS at 2-years and 5-years respectively, which were the values considered plausible by clinicians at the December 2023 UK market access advisory board as discussed in the Original Company Submission (Document B.3.3.2.1).
    - As with PFS, the implausible crossing of hazards/survival curves that are presented in the NMA outputs also translated into implausible crossing of survival curves and therefore implausible predicted outcomes for fruquintinib. It should be noted that this is also the case, and to a greater extent, in the other FP models presented in Appendix C (-3, -2 and -2, -2).
- The regorafenib curve is well aligned with 5-year OS of [redacted]%, compared with 0.4% predicted by the company in TA866 (5)

Therefore, hazards have been capped to model more clinically plausible outcomes, as with PFS (Figure 24). The fruquintinib curve is estimated after capping the hazards at 5 months (set equal to the reference curve at the point of crossing), in line with clinical opinion to the Company in line with clinical opinion to the Company, which stated that greater tumour shrinkage and DCR rates may translate to longer OS, and that PFS benefit would be expected to result in OS benefit. This is therefore considered a conservative assumption. It should be noted that when capping is applied, all FP models produce similar outcomes, and therefore the choice of model has limited impact on results (Appendix C).

Figure 24: FP model; OS – 4L+ scenario (CORRECT reference curve; capped hazards)

Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

With capping, the fruquintinib curve is well aligned with the trial data, and clinical opinion:

- The fruquintinib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]% respectively, compared with 30% in the pooled FRESCO and FRESCO-2 KM data at 1-year
- The fruquintinib curve aligns well with 8–10% and 1% at 2-years and 5-years respectively, which were the values considered plausible by clinicians at the December 2023 UK market

access advisory board as discussed in the Original Company Submission (Document B.3.3.2.1).

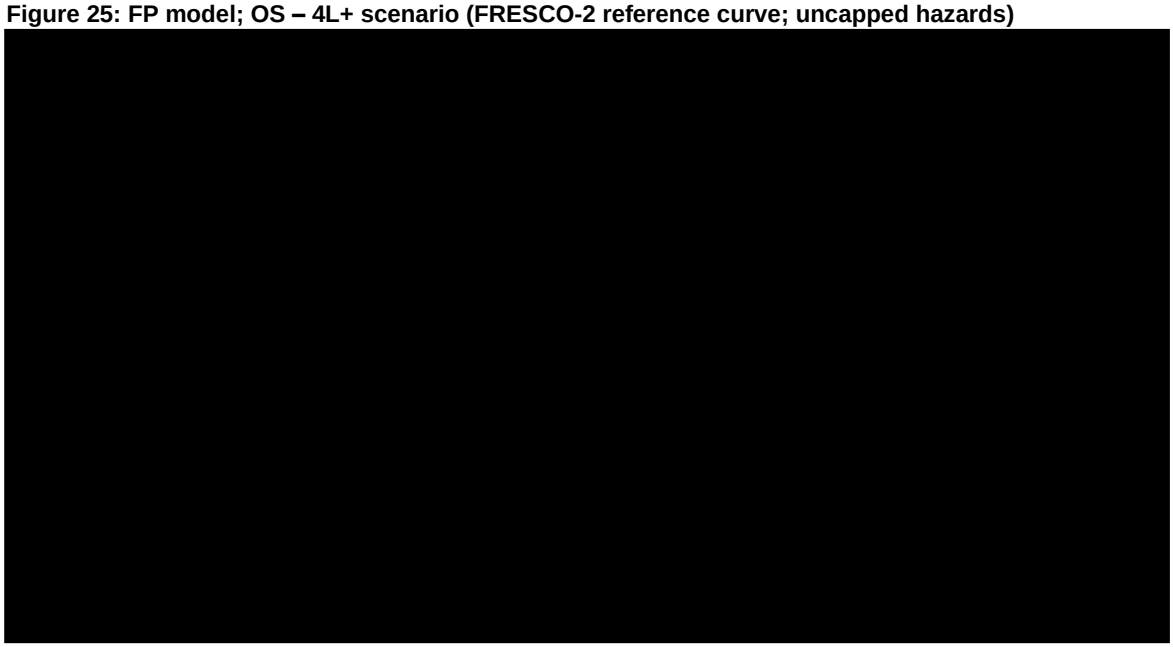
- The median OS (months) is well aligned with FRESCO-2 (7.4 months) and underpredicts the Pooled FRESCO and FRESCO-2 (Median OS of 8.0 months), and Xu (Median OS of 7.7 months) studies by less

Therefore, the -3, -3 FP model overall provides a good fit to the clinical trial data when capping is applied. This further highlights the implausibility of the hazards crossing for fruquintinib and the relevant comparators. Median OS for each curve choice and curves with no capping are presented in Appendix C.

4L+ scenario (fruquintinib reference curve; FRESCO-2 data)

The predicted survival curves for each scenario based on the -3, -3 models are presented in Figure 25. The corresponding curves for the -3, -2 and -2, -2 FP models are provided in the Appendix C.

Figure 25: FP model; OS – 4L+ scenario (FRESCO-2 reference curve; uncapped hazards)



Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

Median estimates for each comparator were compared with reported medians from relevant RCTs, previous modelling approaches throughout this appraisal, and real-world evidence in Table 7.

As expected, median OS for fruquintinib using the FP NMA time-varying HRs (months) is aligned with the median OS from FRESCO-2 (7.4 months), but underpredicts the median OS Xu (7.7 months), FRESCO (9.3 months), and the pooled FRESCO and FRESCO-2 data (8.0 months). For regorafenib, the median OS (months) is relatively aligned with the trial data from pooled CORRECT and CONCUR data (6.9 months) and well aligned with the real-world evidence for regorafenib (5.8–7.6 months). For BSC, the predictions of the median OS using the FP NMA -3, -3 model underpredicted the RCTs slightly (months) compared with a pooled FRESCO and FRESCO-2 median OS of 5.5 months).

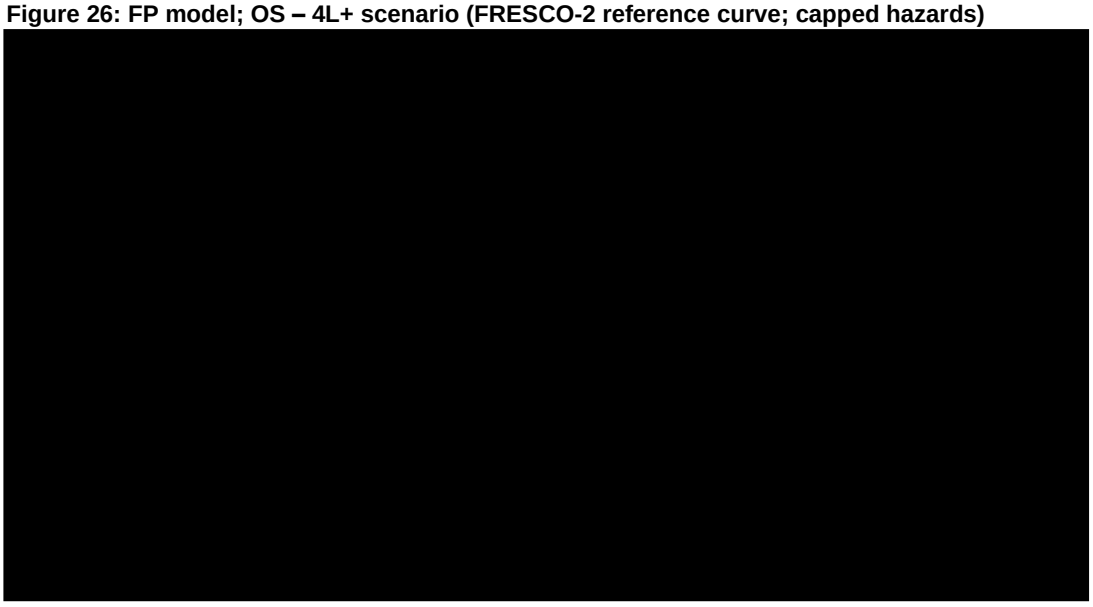
Landmark estimates of survival at 1-year, 2-years and 5-years were also compared with observed data and previous TAs (Table 8):

- The fruquintinib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]%, compared with 30% in the pooled FRESCO and FRESCO-2 KM data at 1-year
    - The fruquintinib curve aligns well with clinical opinion of 8–10% OS and 1% OS at 2-years and 5-years respectively, which were the values considered plausible by clinicians at the December 2023 UK market access advisory board as discussed in the Original Company Submission (Document B.3.3.2.1).
- The regorafenib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]%, respectively, therefore, overestimating survival compared with observed outcomes and clinician estimates.
- As with PFS, the implausible crossing of hazards/survival curves that are presented in the NMA outputs also translated into implausible crossing of survival curves and therefore implausible predicted outcomes for fruquintinib. It should be noted that this is also the case, and to a greater extent, in the other FP models presented in Appendix C (-3,-2 and -2,-2).

Therefore, hazards have been capped to model more clinically plausible outcomes, as with PFS (Figure 26). For this scenario, the regorafenib curve is estimated after capping the hazards at 5 months (set equal to the fruquintinib hazards at the point of crossing), in line with clinical opinion to the Company, which stated that greater tumour shrinkage and DCR rates may translate to longer OS, and that PFS benefit would be expected to result in OS benefit. This is considered to be equivalent methodologically to the scenarios which use regorafenib and trifluridine-tipiracil as the reference curve.

It should be noted that when capping is applied, all FP models produce similar outcomes, and therefore the choice of model has limited impact on results.

Figure 26: FP model; OS – 4L+ scenario (FRESCO-2 reference curve; capped hazards)



Abbreviations: 4L+, fourth-line plus; FP, fractional polynomial; KM, Kaplan Meier; PFS, progression-free survival.

With capping, the regorafenib curves are well aligned with the trial data, and clinical opinion:

- The regorafenib curve predicts 1-year, 2-year and 5-year OS of [redacted]%, [redacted]%, and [redacted]%, respectively, which is more aligned with the predictions from TA866 (27.1% at 1-year and 0.4% at 5-years) than the uncapped hazards

Company response to the Committee's requests following ACM2

Therefore, the -3, -3 FP model overall provided a good fit to the clinical trial data, when capping is applied. This further highlights the implausibility of the hazards crossing for fruquintinib and the relevant comparators. Median OS for each curve choice and curves with no capping are presented in Appendix C.

The outcomes predicted when using the FRESCO-2 data as the reference curve are more closely aligned with the fruquintinib trial data at 2- and 5-years, and more closely align with the 5-year survival estimate presented by the company in TA866 for regorafenib. Therefore, Takeda believe scenario analyses using FRESCO-2 as the reference curve are more appropriate.

Table 7: Comparison of OS outcomes

Approach	Median OS, months
Fruquintinib	
FRESCO (26)	9.3
FRESCO-2 (27)	7.4
Xu, 2012 (28)	7.7
Pooled FRESCO and FRESCO data (11)	8.0
Without capping of hazards	
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve)	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]
With capping of hazards	
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve)	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]
Regorafenib	
CORRECT (29)	6.4
CONCUR (30)	8.8
TA866 model predicted value (5)	7.1
Pooled CORRECT and CONCUR (5, 29, 30)	6.9
REBECCA RWE study (31)	5.6
CORRELATE RWE study (45)	7.7
RECORA RWE study (32)	5.8
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]
Trifluridine-tipiracil	
RECOURSE (33)	7.2
TERRA (25)	7.8
Yoshino (34)	9.0
TA405 model predicted value (3)	7.4
Pooled RECOURSE and Yoshino (3)	7.3
Trifluridine-tipiracil monotherapy reported in SUNLIGHT (6, 46)	7.5
Tong 2021 RWE study (36)	5.8

Stavraka 2021 RWE study (37)	7.6
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]
BSC	
FRESCO (26)	6.6
FRESCO-2 (27)	4.8
Xu, 2012 (28)	5.5
Pooled FRESCO and FRESCO data (11)	5.5
CORRECT (29)	5.0
CONCUR (30)	6.3
Pooled CORRECT and CONCUR (5, 29, 30)	5.3
TA405 model predicted value (3)	5.3
RECOURSE (33)	5.2
TERRA (25)	7.1
Yoshino (34)	6.6
Pooled RECOURSE and Yoshino (3)	5.4
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]

Abbreviations: BSC, best supportive care; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RWE, real-world evidence.

Table 8: Comparison of OS outcomes; landmark stats

Approach	1-year OS	2-year OS	5-year OS
Fruquintinib			
Constant HR NMA	[redacted]	[redacted]	[redacted]
Clinical opinion	30%	8-10%	1%
Pooled FRESCO and FRESCO-2 data (11)	30%	-	-
Without capping of hazards			
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]	[redacted]	[redacted]
With capping of hazards			
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve)	[redacted]	[redacted]	[redacted]
Regorafenib			
Constant HR NMA	[redacted]	[redacted]	[redacted]

Company response to the Committee's requests following ACM2

TA866 model predicted value (5)	27.1%	NR	0.4%
Pooled CORRECT and CONCUR (5, 29, 30)	NR	NR	NR
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; uncapped hazards)	[redacted]	[redacted]	[redacted]
Trifluridine-tipiracil			
RECOURSE (33)	27.1%		
TA405 model predicted value (3)	-	8.3%	0.5%
3L+ Base Case (-3, -3 FP NMA applied to trifluridine-tipiracil SACT curve; capped hazards)	[redacted]	[redacted]	[redacted]
BSC			
FRESCO-2 (27)	23.2%	-	-
Pooled FRESCO and FRESCO-2 data (11)	20.9%	1.0%	0.0%
TA405 predicted	-	4.1%	0.6%
TA866 predicted	18.1%	-	1.1%
Clinical opinion	-	-	0%
4L+ scenario analysis A (-3, -3 FP NMA applied to digitised CORRECT curve; capped hazards)	[redacted]	[redacted]	[redacted]
4L+ scenario analysis B (-3, -3 FP NMA applied to FRESCO-2 reference curve; capped hazards)	[redacted]	[redacted]	[redacted]

Abbreviations: BSC, best supportive care; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; RWE, real-world evidence.

Summary of results of the FP NMA

Based on the assessment of model selection, the FE second-order -3, -3 FP NMA model was considered the best choice for the extrapolation of OS and PFS curves from the options available, based on:

- The -3, -3 model provided the best statistical fit out of all FP NMA models explored (lowest DIC) for both OS and PFS
- The FE and RE models were within three DIC points for the -3, -3 FP model for both OS and PFS. The FE models were considered more appropriate than the RE models, which are associated with challenges regarding the convergence of models and lack of statistical heterogeneity found between trials in the direct meta-analysis.
- It was difficult to assess predictive accuracy of the FP models: it was concluded that all explored models were similar in predictive accuracy

Company response to the Committee's requests following ACM2

	• All FP models produced hazards over time that lacked face validity, however the -3, -3 FP models resulted in the most plausible estimates out of the models explored:
	
	However, there remain a number of uncertainties with the FP NMA analysis.
	
	Importantly, all PFS and OS FP models, including the preferred -3,-3 FP model, predicted implausible crossing of the hazards between the fruquintinib curve and the active comparators. Clinical expert opinion obtained by the Company stated that greater tumour shrinkage and DCR rates observed with fruquintinib treatment may be expected to translate to longer OS, and that PFS benefit would be expected to be correlated with OS benefit. All models were therefore considered to predict implausible outcomes. Recent NMAs reported in the literature using FP models have been deemed uncertain as the analysis results obtained also suffered from face validity issues relating to clinically implausible extrapolations of survival (20).
	
	In addition, the predicted survival outcomes for fruquintinib based on the FP NMA severely underestimate the pooled FRESCO and FRESCO-2 data. And, given the predicted regorafenib and trifluridine-tipiracil outcomes align well with the observed data, the relative benefit of fruquintinib vs active comparators is highly underestimated. It should also be noted that outcomes for the 4L+ scenario are very similar (within 0.5%) or better than the 3L+ base case, which lacks face validity.
	
	FP NMAs have been reported to predict clinically implausible crossing of curves in other prior NICE appraisals (38, 39, 44). Therefore, as previously described, a cap on the hazards was explored, as also previously reported in oncology modelling in prior NICE TAs (43, 44). In TA739, the EAG initially raised concerns around the Company's approach of capping the HRs due to implausible hazards, however, the EAG ultimately stated in their report that "this raises questions about whether the results from the fractional polynomial models used in the network meta-analysis are appropriate to inform the economic analyses if it is necessary to cap them in order to provide plausible results" (43). In TA858, the results from the Company's FP NMA were considered to be highly uncertain, and difficult to interpret. The final appraisal document states that "the EAG prefers a proportional hazards network meta-analysis despite uncertainty about whether the proportional hazards assumption holds", the Committee subsequently concluded that "both approaches are associated with uncertainty, but the results of the EAG's proportional hazards NMAs could be used for decision making" (40).
	
	Takeda appreciate that a cap of the hazards is sub-optimal. However, Takeda believe that the only alternative is a rejection of the appropriateness of FP's as also concluded in TA739 (43), and an assumption of PH throughout (using the standard NMA). Takeda therefore believe that the cap provides a plausible scenario in response to Committee Request 3, where the PH assumption is relaxed. Survival curves for fruquintinib with the cap imposed align well with median OS and landmark OS estimates from the relevant RCTs, clinical opinion, and RWE. The cap is also applied for PFS, however this has a minor impact on the resultant survival curves.
	
	Other limitations in the analysis include:
	
	• Uncertainties remain when applying HRs to reference curves that are estimated by digitising KM data
	  ○ Data for trifluridine-tipiracil is taken from different sources for OS (SACT) and PFS (Pooled RECOURSE and Yoshino)
	  ○ The model/NMA was not able to incorporate the pooled CORRECT and CONCUR KM data for regorafenib as only KM data from the individual trials was available. This is also the case for the pooled RECOURSE, Yoshino and TERRA data.
	  ○ This was discussed as part of comment number 6 in the draft guidance response

Company response to the Committee's requests following ACM2

	• Fractional polynomials have been used in prior oncology appraisals and uncertainties around heterogeneity in the indirect treatment comparison have been highlighted (48, 49) ○ Fractional polynomials were considered in TA858 (lenvatinib with pembrolizumab for advanced renal cell carcinoma) but the EAG preferred a PH network despite uncertainty around whether the PH holds due to results from the FP NMA being uncertain and difficult to interpret (40) Cost-effectiveness results are presented in Appendix B (base-case pairwise results vs regorafenib) and Appendix A (Committee requested scenarios by line of therapy). Crucially, in the updated base-case analysis, and all of the scenario analyses across lines of therapy, fruquintinib remains dominant in the pairwise comparison vs regorafenib (the key comparator in this appraisal). In the 3L+ population, the incremental NHB increases from [redacted] to [redacted] when switching from the standard Bayesian NMA assuming PH, to the FP NMA approach. In the 4L+ scenario using FRESCO-2 as the reference curve, the incremental NHB of fruquintinib vs regorafenib increases from [redacted] to [redacted] when switching from the standard Bayesian NMA assuming PH, to the FP NMA approach. In the 4L+ scenario using CORRECT as the reference curve, the incremental NHB of fruquintinib vs regorafenib remains [redacted] when switching from the standard Bayesian NMA assuming PH, to the FP NMA approach. Importantly, the severity modifier remains 1.7 across all of the scenarios considered. **Conclusion** Takeda appreciates the uncertainties in the original constant HR NMA approach given uncertainty in whether the PH assumption holds. Takeda have also highlighted that the FP NMA approach is associated with significant uncertainties. Regardless, the FP NMA has been incorporated into the Company base case in order to show Takeda's flexibility to reduce uncertainty in the modelling assumptions and commitment to achieving a positive recommendation for patients with mCRC in this area of high unmet need. The cost-effectiveness results of the FP NMA show that the relaxation of the PH assumption should no longer be a decision limiting factor in this appraisal, with fruquintinib remaining dominant vs the key comparator regorafenib in both the 3L+ and 4L+ scenarios The Company believe that this analysis, alongside a revision to the PAS for fruquintinib (outlined in Appendix B) serves to reduce the uncertainty in the assumptions of the model to a level that is considered acceptable for decision making. The Company are aware that a confidential PAS discount exists for regorafenib and believe that fruquintinib is a cost-effective use of resources at an indicative WTP threshold of £25,000 per QALY when a reasonable comparator PAS assumption is included..
4	**Utility values** The draft guidance stated that, as opposed to the original Company base case of sourcing utility values from the FRESCO-2 trial directly, they *"considered that pooling all the available utility values would have provided useful additional data for decision-making, but in the absence of this the CORRECT trial utility values were likely to be a plausible approximation of the pooled estimate*". Therefore, in response to the draft guidance, the Company updated the base case to use the utility values from CORRECT as per the Committee's preference. Since the Committee's additional requests following ACM2, the Company have now updated these utility values to reflect the Committee's preference to use the pooled FE utilities in the 3L+ population.

Company response to the Committee's requests following ACM2

As noted by the External Assessment Group (EAG), the values estimated from the SUNLIGHT study are substantially higher than previous appraisals in 3L+ mCRC, and therefore may overestimate HRQoL (6). The Committee in TA1008 also noted that other sources of utility values, including the CORRECT study, offer more appropriate estimates of absolute utility associated with patients with 3L+ mCRC than using data from SUNLIGHT. A further scenario has therefore been conducted that estimates a fixed effects NMA including only FRESCO-2 and CONCUR/CORRECT pooled values, therefore removing the utility values estimated from SUNLIGHT that may overestimate utility in this patient population.

The Company have also updated utilities in the 4L+ scenario to data from FRESCO-2 to reflect the updated Committee preference post-ACM2.

As detailed in Request 1, the Company have provided the requested analyses for the 3L+ and 4L+ populations separately, but maintain that an unrestricted 3L+ population is most appropriate for decision-making.

3L+

The Company maintain that using the pooled fixed effects NMA utility values to inform the 3L+ economic analysis may overestimate health related quality of life (HRQoL) in this population, however, to demonstrate flexibility, the Company have included these utility values in the updated base case as per the Committee's request. The pooled analysis requested by the Committee includes data from FRESCO-2 (4), CONCUR and CORRECT pooled data (5), and SUNLIGHT (6), as presented in Table 9. The pooled estimates with SUNLIGHT excluded from the fixed effects meta-analysis are presented in Figure 27 and Figure 28 for progression-free and progressed disease, respectively.

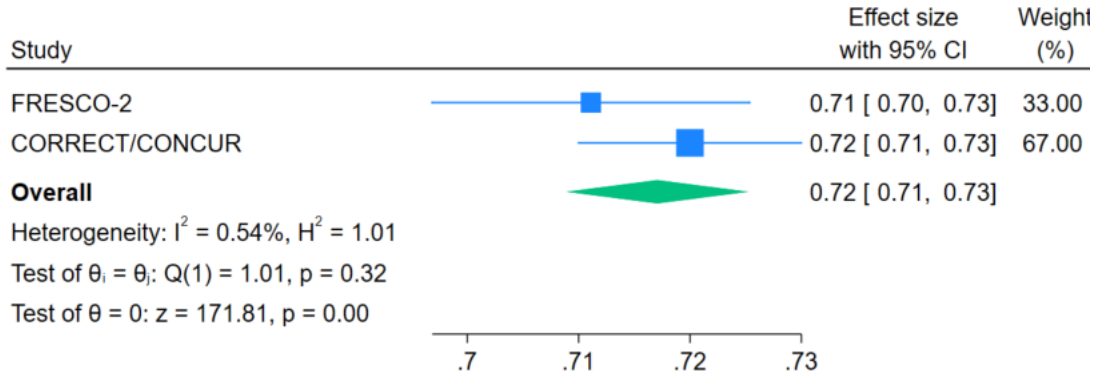
Table 9: Utility values from relevant mCRC trials

Trial	Progression-free (95% CI), n	Progressed (95% CI), n
FRESCO-2 (4)	0.71 (0.70, 0.73) 1,455	0.65 (0.62, 0.69) 326
CONCUR/CORRECT pooled (5)	0.72 (0.71, 0.73) 2,600	0.59 (0.56, 0.62) 570
SUNLIGHT (6)	0.76 (0.73, 0.79) 1,975	0.68 (0.65, 0.71) 304

Abbreviations: CI, confidence interval; mCRC, metastatic colorectal cancer.

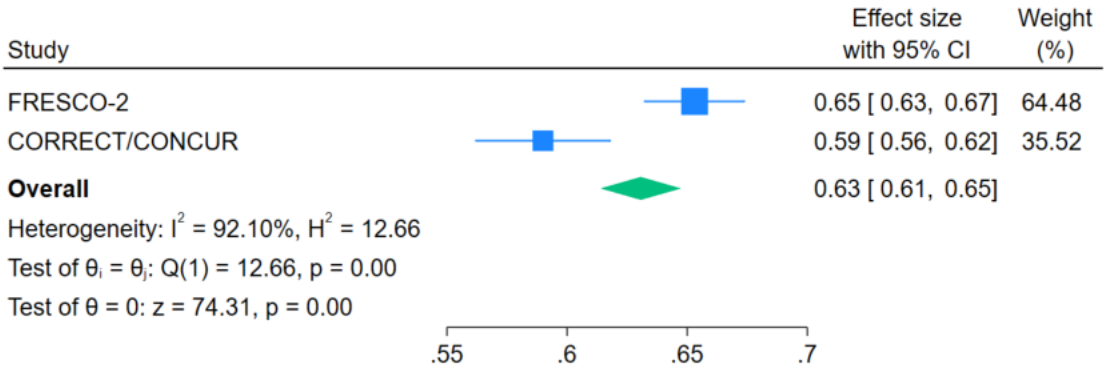
Company response to the Committee's requests following ACM2

Figure 27: Results of utility value meta-analysis, progression-free, FE model, excluding SUNLIGHT



Abbreviation: CI, confidence interval; FE, fixed effects.

Figure 28: Results of utility value meta-analysis, progressed, FE model, excluding SUNLIGHT



Abbreviation: CI, confidence interval; FE, fixed effects.

To summarise, despite the potential overestimation of utility, the Company have updated the base case to use utility values from:

- Fixed effects NMA including FRESCO-2 (4), CORRECT/CONCUR (5), and SUNLIGHT (6)

A further scenario analysis is provided in the 3L+ population, which excludes SUNLIGHT:

- Fixed effects NMA including FRESCO-2 (4) and CORRECT/CONCUR (5)

In both scenarios fruquintinib remains dominant compared with regorafenib, with the NHB remaining consistent across scenarios and the impact of removing SUNLIGHT from the pooled FE utilities is small, due to the relatively low weight assigned to the SUNLIGHT values in the meta-analysis. Results of the updated base case are presented in Appendix B. The results for all of the Committee requested analyses are presented in Appendix A.

4L+

The Company agree with the Committee that the most appropriate source of utility data to inform the 4L+ scenario is FRESCO-2. Therefore, these data are used to inform the requested scenario analysis at 4L+. The results of this scenario analysis are presented in Appendix A.

A summary of the utility values used in the base case and scenario analysis is provided in Table 10.

Company response to the Committee's requests following ACM2

Table 10: Updated utility values

Health state	Progression-free	Progressed
FRESCO-2 regression model (original company submission)	0.71	0.65
CORRECT absolute values (draft guidance) (3)	0.73	0.59
3L+		
Meta-analysis FE (Updated base case)	0.72	0.64
Meta-analysis FE excluding SUNLIGHT (Scenario analysis)	0.72	0.63
4L+		
FRESCO-2 regression model	0.71	0.65

Abbreviations: FE, fixed effects.

5 **Explore alternative approach to relative dose intensity (RDI)**

Although the Company consider there to be uncertainty regarding the most appropriate relative dose intensity for each comparator, the Company are willing to accept the Committee's preferred assumption in the draft guidance, adopting treatment-specific RDI estimates from the relevant clinical trials for all treatments. This assumption has been updated in the base case and all additional scenario analyses requested by the Committee.

The updated base case results are presented in Appendix B.

6 **Update mean starting age as per the systemic anti-cancer therapy (SACT) data**

The Committee have requested that following updates are made to the mean age used in the model for the 3L+ and 4L+ analyses:

- ***3L+:*** The mean age should be equal to the mean age for patients receiving trifluridine-tipiracil from the SACT data provided during ACM2 (64.3 years)
- ***4L+:*** The mean age should be equal to the mean age for patients receiving regorafenib from SACT data provided during ACM2 (64.7 years)

As detailed in Request 1, the Company have provided the requested analyses for the 3L+ and 4L+ populations separately, but maintain that an unrestricted 3L+ population is most appropriate for decision-making. Additionally, the Company maintain that the SACT data may overestimate the mean age of patients expected to receive fruquintinib in clinical practice, and that the most appropriate estimate of mean age of patients expected to receive fruquintinib in UK clinical practice is the midpoint between the SACT data and the pooled FRESCO and FRESCO-2 clinical trial data. Despite this, to demonstrate flexibility, the Company have included the SACT mean starting age in the updated base case.

The Company does not have access to further information on the SACT dataset and importantly, there are no data available on the baseline characteristics of the patient population that these data are based on. Given no detail is available on baseline characteristics beyond mean age, the Company are therefore unable to verify whether the population aligns with the population expected to receive fruquintinib in clinical practice in the UK. Furthermore, the SACT data are in patients currently receiving trifluridine-tipiracil monotherapy, which reflects the population who are now likely to be treated with trifluridine-tipiracil in combination with bevacizumab. As previously mentioned in the response to Request 2, fruquintinib is expected to be used in patients who are not eligible for trifluridine-tipiracil in combination with bevacizumab in the 3L+ setting and hence the SACT patient population may not be appropriate to inform 3L+ modelling for fruquintinib.

Company response to the Committee's requests following ACM2

	The mean age from the pooled FRESCO and FRESCO-2 data (59.4 years) (11) was used in the original Company base case as this aligns with several key data sources: the clinical data informing the appraisal; the median age from real-world evidence (RWE) on fruquintinib use in China (55–61 years); the weighted average of medians across 9 randomised controlled trials (RCTs) in this population (61.1 years); and the mean age accepted in TA866 (60 years) in the same patient population (5) (Appendix C). Furthermore, during the UK market access advisory board, clinical experts stated that the baseline characteristics from the pooled FRESCO and FRESCO-2 data were reflective of the population expected to receive fruquintinib in UK clinical practice (8). The Company believe that the analysis requested by the Committee (using ages of 64.3 years and 64.7 years for the 3L+ and 4L+ scenarios, respectively) likely overestimate the average age in this population. The Company maintain that the Committee-requested values for age represent an upper extreme value, however, to demonstrate flexibility, have included the SACT mean starting age in the updated base case and scenario analyses (64.3 years and 64.7 years in the 3L+ and 4L+ populations, respectively). The Company expect the true values for mean age in both populations lie between the SACT data and the pooled FRESCO and FRESCO-2 mean age (59.4 years). Full results of all scenario analysis are presented in Appendix A. The updated base case results are presented in Appendix B. Crucially, all Committee requested scenarios including the SACT mean starting age in the 3L+ and 4L+ scenarios, result in a QALY severity modifier of 1.7x. The impact on the ICER of using the mean starting ages from SACT is small.
7	**At 4L+, regorafenib should be used as the reference curve: OS sourced from SACT and PFS based on data previously used in the model** The Committee requested that regorafenib should be the reference curve for the 4L+ analysis. The Committee originally requested that the regorafenib OS curve be sourced from SACT and the PFS curve be based on data previously in the model. However, as communicated on 30th January 2025, the Committee acknowledged the additional time required for new SACT and, to avoid delay to patient access through this request, considered that the regorafenib clinical trial data could be used as the OS reference curve as opposed to SACT data. As detailed in Request 1, the Company has provided the requested analyses for the 3L+ and 4L+ populations separately, but maintain that an unrestricted 3L+ population is most appropriate for decision-making. Nonetheless, the Company explored the availability of regorafenib SACT data via the National Health Service (NHS) Data Access Request Service (DARS), however the Company were informed that obtaining the data would likely take up to 10 months, meaning the data would not be available to incorporate into the economic model until the end of 2025. Following discussions with the Associate Director of NICE Committee B on 6th March, it was agreed that "obtaining SACT OS data for regorafenib will not be possible" and is therefore not required in this response. Therefore, for the 4L+ scenario analysis, the Company have provided results using regorafenib as the reference curve at 4L+ sourced from published regorafenib data. Only published CORRECT data are available to inform the regorafenib reference curve as per the Committee's preference (29). However, the Company does not consider this appropriate as this would mean that the data used to inform the 4L+ analysis: • Does not align with a 4L+ population, as it is based on a reference curve at 3L+ (CORRECT). The CORRECT data is in a 3L+ population and 27% of patients in the CORRECT trial received fewer than three previous lines of therapy. • Does not use the totality of evidence available for regorafenib. As only OS and PFS data from either CORRECT or CONCUR (i.e. not pooled) were available for regorafenib, this scenario does not align with the Committee's preferred assumptions for modelling regorafenib at 3L+ (both CORRECT and CONCUR are considered relevant RCTs and inform the NMA), therefore introducing uncertainty into the analysis.

Company response to the Committee's requests following ACM2

	• Is not based on individual patient data (IPD) as per the original Company base case, as it is based on digitised published KM data, which is associated with a higher margin for error in the estimation of patient outcomes. The Company therefore believe that using the FRESCO-2 data alone would be more appropriate than using the CORRECT data as the reference curve for the 4L+ scenario requested by the Committee. Importantly, FRESCO-2 captures data in a patient population who have previously received either trifluridine-tipiracil or regorafenib, which mirrors how fruquintinib is expected to be used at 4L+ (4, 29). In the 4L+ scenario analysis, the Company therefore prefer the use of FRESCO-2 data to inform the reference curves for OS and PFS, as opposed to the Committee's preference for the 3L+ regorafenib data from CORRECT. For this scenario analysis, the selected OS, PFS and TTD curves based on FRESCO-2 are in line with the curves chosen as part of the Company response to EAG clarification question B4: the generalised gamma distribution was chosen for OS, and the log-normal distribution was selected for both PFS and TTD based on statistical and visual fit to the data and alignment with clinical expert opinion. Alternative distributions can be explored within the cost-effectiveness model. However, to ensure the Committee's requests are adequately addressed, scenario analyses are also presented that use the digitised CORRECT OS and PFS data for regorafenib to inform the reference curves. For this scenario analysis, the selected OS and PFS curves based on CORRECT are in line with the curves chosen as part of the Company response to EAG clarification question B3: the generalised gamma distribution was chosen for OS, and the log-normal distribution was selected for PFS based on statistical and visual fit to the data and alignment with clinical expert opinion. Alternative distributions can be explored within the cost-effectiveness model. Full results of the Committee's requested analysis are presented in Appendix A. Based on the Committee's requested analyses, fruquintinib remains dominant compared with regorafenib. The Company would like to reiterate that the 3L+ population is considered the most appropriate for decision-making, therefore the separate 4L+ scenario is not incorporated into the updated base case. Fruquintinib remains dominant vs regorafenib in the 4L+ scenario regardless of whether the FRESCO-2 or CORRECT reference curve is used, and similar results are produced vs the 3L+ base case with respect to NHB.
8	**The severity modifier should be calculated using these preferences** As per the Committee's request, the Company have provided updated severity modifier calculations based on the Committee's preferred assumptions. The following updates have been made to the calculations: 3L+ base case: • Fractional polynomial NMA HRs applied vs. trifluridine-tipiracil reference curve (SACT for OS and Pooled RECOURSE and Yoshino for PFS) • Utility values sourced from the pooled fixed effects analysis • Treatment-specific RDI estimates • Updated mean starting age as per the SACT data for 3L patients (64.30 years) 4L+ scenario: • Fractional polynomial NMA HRs applied vs fruquintinib reference curve (FRESCO-2 trial; a scenario where CORRECT is used as the reference curve is presented in Appendix A) • Utility values sourced from the FRESCO-2 trial • Treatment-specific RDI estimates • Updated mean starting age as per the SACT data for 3L patients (64.70 years) All other assumptions remain as per the base-case broader 3L+ population. A full summary of severity modifier calculations by scenario are presented in Appendix A.

Company response to the Committee's requests following ACM2

As detailed in Request 1, the Company has provided the requested analyses for the 3L+ and 4L+ populations separately, but maintain that an unrestricted 3L+ population is most appropriate for decision-making. Importantly, the 1.7x severity modifier is indicated in the updated base case and across all considered scenario analyses.

3L+

Methods for calculating the updated severity modifier are as per those described in Section B.3.7 of the Company submission. The resulting absolute shortfall was [redacted] and [redacted] vs regorafenib and trifluridine-tipiracil, respectively, and the resulting proportional shortfall was [redacted]%, and [redacted]% vs regorafenib and trifluridine-tipiracil, respectively, when using a starting age of 59.4 years. The resulting absolute shortfall was [redacted] and [redacted] vs regorafenib and trifluridine-tipiracil, respectively, and the resulting proportional shortfall was [redacted]%, and [redacted]% vs regorafenib and trifluridine-tipiracil, respectively when using a starting age of 64.3 years. A summary of the calculations is presented in Table 11.

As per the response to Request 6, the Company consider the most appropriate starting age to lie between the submitted Company base case (59.4 years), and the SACT data (64.3 years). Therefore, the Company consider the true QALY shortfall estimates to be between the two results based on these ages. This suggests that a 1.7x QALY severity multiplier is reasonable across all analyses. Critically, in all scenario analyses conducted, the severity modifier remains 1.7 vs regorafenib and trifluridine-tipiracil, demonstrating the robustness of the severity modifier estimates to changing assumptions.

Table 11: Summary of updated QALY shortfall analysis at 3L+

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall†
Starting age: 59.4 years		
12.89	Regorafenib: [redacted] Trifluridine-tipiracil: [redacted]	[redacted] [redacted]
Starting age: 64.3 years		
11.16	Regorafenib: [redacted] Trifluridine-tipiracil: [redacted]	[redacted] [redacted]

†The 1.7 severity modifier is indicated when the absolute QALY shortfall ≥ 18 or the proportion QALY shortfall ≥ 95%

Abbreviations: QALY, quality-adjusted life year; 3L+, third-line plus.

4L+

The resulting absolute shortfall was [redacted] and [redacted] vs regorafenib and BSC, respectively, and the resulting proportional shortfall was [redacted]%, and [redacted]% vs regorafenib and BSC, respectively, when using a starting age of 59.4 years. The resulting absolute shortfall was [redacted] and [redacted] vs regorafenib and BSC, respectively, and the resulting proportional shortfall was [redacted] %, and [redacted]% vs regorafenib and BSC, respectively when using a starting age of 64.7 years. A summary of the calculations is presented in Table 12.

As per the response to Request 6, the Company consider the most appropriate starting age to be between the submitted Company base case (59.4 years), and the SACT data (64.7 years). Therefore, the Company consider the true QALY shortfall estimates to be between the two results based on these ages. This suggests that a 1.7x QALY severity multiplier is reasonable across all analyses. Critically, in all scenario analyses conducted, the severity modifier remains 1.7 vs regorafenib and BSC, demonstrating the robustness of the severity modifier estimates to changing

Company response to the Committee's requests following ACM2

assumptions. A full summary of severity modifier calculations by scenario are presented in Appendix A.

Table 12: Summary of updated QALY shortfall analysis at 4L+

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall†
Starting age: 59.4 years		
12.89	Regorafenib: [redacted] BSC: [redacted]	[redacted]
Starting age: 64.7 years		
11.16	Regorafenib: [redacted] BSC: [redacted]	[redacted]

†The 1.7 severity modifier is indicated when the absolute QALY shortfall ≥ 18 or the proportion QALY shortfall ≥ 95%

Abbreviations: BSC, best supportive care; QALY, quality-adjusted life year; 4L+, fourth-line plus.

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Company response to the Committee's requests following ACM2

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Company response to the Committee's requests following ACM2

Appendix A: Committee requested analysis results

A summary of results of the Committee requested analyses at 3L+ are presented in Table 18 and are calculated at the updated proposed patient access scheme (PAS) price for fruquintinib outlined in Appendix B. The Company believe that the relevant population for the base case analysis is 3L+ as per the marketing authorisation. As noted throughout the original Company submission and this document, regorafenib is considered the most relevant comparator for decision making. This is based on how the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib, as discussed in the response to Request 2. Pairwise results vs trifluridine-tipiracil are also presented as per the Committee's request.

The additional analyses requested by the Committee had minimal impact on the incremental NHB of fruquintinib vs regorafenib, with NHB considered to be the most appropriate outcome given the sensitivity of incremental cost-effectiveness ratio (ICER) estimates due to small incremental QALYs. NHB was calculated at a WTP threshold of £25,000 per QALY in line with NICE preferences. Based on the committee's requested analyses, fruquintinib remains dominant compared with regorafenib. Results of severity modifier calculations are presented in Table 14. Fruquintinib is associated with a proportional QALY shortfall of greater than 0.95, and therefore is associated with a severity modifier of 1.7 in the comparison vs regorafenib and trifluridine-tipiracil.

Company response to the Committee's requests following ACM2

Table 13: Summary of updated scenario analysis results, 3L+ (PAS price) – Cumulative scenarios

Cumulative scenarios	Fruquintinib vs regorafenib				Fruquintinib vs trifluridine-tipiracil			
	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £25,000 WTP threshold	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £25,000 WTP threshold
Company base case at ACM2	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case at ACM2 (with updated PAS)	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 6: SACT starting age	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 3: FP NMA	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 5: Treatment-specific RDI	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 4: Committee preferred utility values (Pooled FE meta-analysis) **[Committee requested results]**	[redacted]	[redacted]	**dominant**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario based on Request 4: utility values based on the pooled FE meta-analysis excluding SUNLIGHT	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Adjusted with a severity modifier of 1.7 in line with calculations in the model.
Abbreviations: ACM2, Appraisal Committee Meeting 2; FE, fixed effects; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; PAS, patient access scheme; QALYs, quality-adjusted life years; RDI, relative dose intensity; SACT, systemic anti-cancer therapy; WTP, willingness-to-pay threshold; 3L+, third-line plus.

Company response to the Committee's requests following ACM2

Table 14: Summary of updated severity modifier calculations, 3L+ - Cumulative scenarios

Cumulative scenarios	Fruquintinib vs regorafenib				Fruquintinib vs trifluridine-tipiracil			
	Regorafenib QALYs	Absolute shortfall	Proportional shortfall	Weighting	Trifluridine-tipiracil QALYs	Absolute shortfall	Proportional shortfall	Weighting
Company base case at ACM2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 6: SACT starting age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 3: FP NMA	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 5: Treatment-specific RDI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 4: Committee preferred utility values (Pooled FE meta-analysis) **[Committee requested results]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario based on Request 4: utility values based on the pooled FE meta-analysis excluding SUNLIGHT	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM2, Appraisal Committee Meeting 2; FE, fixed effects; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; QALYs, quality-adjusted life years; RDI, relative dose intensity; SACT, systemic anti-cancer therapy; WTP, willingness-to-pay threshold; 3L+, third-line plus.

Company response to the Committee's requests following ACM2

A summary of the results of the Committee requested analyses at 4L+ are presented in Table **15**. As noted throughout the original Company submission and this document, regorafenib is considered the most relevant comparator for decision making. This is based on how the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib, as discussed in the response to Request 2. Pairwise results vs BSC are also presented as per the Committee's request. Results are presented that use the CORRECT data to inform the reference curve, however the Company consider the scenario where FRESCO-2 is the reference curve to be more appropriate, as discussed in response to Request 7.

The additional analyses requested by the Committee had minimal impact on the incremental NHB of fruquintinib vs regorafenib, with NHB considered to be the most appropriate outcome given the sensitivity of ICER estimates due to small incremental QALYs. Based on the committee's requested analyses, fruquintinib remained dominant compared with regorafenib. Results of severity modifier calculations are presented in Table **16**. Fruquintinib is associated with a proportional QALY shortfall of greater than 0.95 and therefore is associated with a severity modifier of 1.7 in the comparison vs regorafenib and BSC.

Company response to the Committee's requests following ACM2

Table 15: Summary of updated scenario analysis results, 4L+ (PAS price) – cumulative scenarios

Cumulative scenarios	Fruquintinib vs regorafenib				Fruquintinib vs BSC			
	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £25,000 WTP threshold	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £25,000 WTP threshold
Company base case at ACM2 – 3L+ population	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Company base case at ACM2 (with updated PAS) – 3L+ population	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 6: SACT starting age	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 3: FP NMA (CORRECT as the reference curve)	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 5: Treatment-specific RDI	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 4: Committee preferred FRESCO-2 utilities **[Committee requested results]**	[redacted]	[redacted]	**dominant**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario based on change to Request 3: FP NMA (FRESCO-2 as the reference curve) **[Company preferred approach]**	[redacted]	[redacted]	dominant	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

†Adjusted with a severity modifier of 1.7 in line with calculations in the model.
Abbreviations: ACM2, Appraisal Committee Meeting 2; BSC, best supportive care; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; PAS, patient access scheme; QALYs, quality-adjusted life years; RDI, relative dose intensity; SACT, systemic anti-cancer therapy; WTP, willingness-to-pay threshold; 4L+, fourth-line plus.

Company response to the Committee's requests following ACM2

Table 16: Summary of updated severity modifier calculations, 4L+ - Cumulative scenarios

Cumulative scenarios	Fruquintinib vs regorafenib				Fruquintinib vs BSC			
	Regorafenib QALYs	Absolute shortfall	Proportional shortfall	Weighting	BSC QALYs	Absolute shortfall	Proportional shortfall	Weighting
Company base case at ACM2 (with updated PAS) – 3L+ population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 6: SACT starting age	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 3: FP NMA (CORRECT as the reference curve)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 5: Treatment-specific RDI	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Request 4: Committee preferred FRESCO-2 utilities **[Committee requested results]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario based on change to Request 3: FP NMA (FRESCO-2 as the reference curve) **[Company preferred approach]**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ACM2, Appraisal Committee Meeting 2; FP, fractional polynomial; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; NMA, network meta-analysis; QALYs, quality-adjusted life years; RDI, relative dose intensity; SACT, systemic anti-cancer therapy; WTP, willingness-to-pay threshold; 4L+, fourth-line plus.

Company response to the Committee's requests following ACM2

In order to reflect the expected use of fruquintinib in a broad 3L onwards population in practice, a scenario analysis is presented in Table 17 where the Committee's preferred 3L+ base case (3a in Table 13) and the 4L+ scenario B3 in Table 15 are combined to produce a weighted ICER for fruquintinib vs regorafenib. The weighting is applied to total costs and QALYs in the model. In line with the Committee's opinion that a small proportion (<10%) of patients will not be suitable for treatment with trifluridine-tipiracil in combination with bevacizumab at 3L and will therefore be eligible for treatment with fruquintinib in this setting (3L), the weighting used for this scenario is 10% for the 3L+ population, and 90% for the 4L+ population, where fruquintinib is expected to replace the use of regorafenib. Results highlight that whilst it has been shown that fruquintinib is dominant in a pairwise comparison with regorafenib across separate 3L+ and 4L+ scenarios, the weighted ICER between scenarios may be more relevant to decision making given the different displacement of comparators across lines in clinical practice. When considering a weighted ICER, fruquintinib is also dominant in a pairwise comparison vs regorafenib.

Table 17: Weighted scenario analysis between 3L+ and 4L+; pairwise vs regorafenib

Technologies	Incremental costs	Incremental QALYs†	Pairwise ICER	Incremental NHB at £25,000 WTP threshold
3L+ Committee preferred base case (Assumptions outlined in response to Request 1)	[redacted]	[redacted]	dominant	[redacted]
4L+ Committee preferred base case but with FRESCO-2 reference curve (Assumptions outlined in response to Request 1)	[redacted]	[redacted]	dominant	[redacted]
Weighted CE results (10% 3L+ and 90% 4L+)	[redacted]	[redacted]	dominant	[redacted]

†Adjusted with a severity modifier of 1.7 in line with calculations in the model.
Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; NHB, net health benefit; QALY, quality adjusted life year; WTP, willingness-to-pay threshold; 3L+, third-line plus; 4L+, fourth-line plus.

Company response to the Committee's requests following ACM2

Appendix B: Updated base case

The Company have updated the base case to align with all of the Committee's preferred assumptions apart from splitting results into 3L+ and 4L+ populations, which has instead been provided in scenario analyses (Appendix A). The updated base case includes:

- Using FPs for the NMA (relaxing the PH assumption) - Request 3
- Using utility values sourced from the pooled FE analysis - Request 4
- Using treatment specific RDI - Request 5
- Updating the mean starting age to that of SACT - Request 6

Takeda have also submitted an enhanced patient access scheme (PAS), which has been accepted by Patient Access Scheme Liaison Unit (PASLU). This is [redacted].

As noted throughout the original Company submission and this document, regorafenib is considered the most relevant comparator for decision making. This is based on how the majority of fruquintinib use in UK clinical practice is expected to replace the use of regorafenib. Furthermore, the Company believe the relevant population for the base case analysis is 3L+ as per the marketing authorisation.

In the base case (including the proposed updated PAS price), fruquintinib was associated with cost savings of [redacted] and an incremental QALY gain of 0.07 vs regorafenib (Table 18), meaning fruquintinib was dominant when compared with regorafenib. Fruquintinib is associated with an incremental NHB of [redacted] vs regorafenib. Takeda are aware that a confidential PAS is also in place for regorafenib, however Takeda believe that fruquintinib is cost-effective at a WTP threshold of £25,000 per QALY when factoring in a range of reasonable comparator confidential PAS discount assumptions. Results are also presented vs trifluridine-tipiracil in Table 19.

The results of these analysis demonstrate that fruquintinib is a cost-effective use of NHS resources for patients with previously treated mCRC, and a positive NICE recommendation for fruquintinib would provide patients and clinicians with a convenient, alternative, oral treatment option with a manageable safety profile, which does not negatively impact quality-of-life.

Company response to the Committee's requests following ACM2

Table 18: Base case results (pairwise analysis vs regorafenib, 3L+) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (fruquintinib vs comparator) (£)	Incremental LYG (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator; severity modifier applied)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £25,000 WTP threshold (fruquintinib vs comparator)
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	-	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year; WTP, willingness-to-pay threshold; 3L+, third-line plus.

Table 19: Base case results (pairwise analysis vs trifluridine-tipiracil, 3L+) – PAS price

Technologies	Total costs (£)	Total QALYs	Incremental costs (fruquintinib vs comparator) (£)	Incremental LYG (fruquintinib vs comparator)	Incremental QALYs (fruquintinib vs comparator; severity modifier applied)	Pairwise ICER (fruquintinib vs comparator)	Incremental NHB at £25,000 WTP threshold (fruquintinib vs comparator)
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fruquintinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; PAS, patient access scheme; QALY, quality adjusted life year; WTP, willingness-to-pay threshold; 3L+, third-line plus.

Company response to the Committee's requests following ACM2

As presented in the response to Request 8, the severity modifier calculations were updated for the updated Company base case. Methods for calculating the updated severity modifier are as per those described in Section B.3.7 of the Company submission. The resulting absolute shortfall was [redacted] vs regorafenib and trifluridine-tipiracil, respectively, and the resulting proportional shortfall was [redacted]% vs regorafenib and trifluridine-tipiracil, respectively. A summary of the calculations is presented in Table 20.

Critically, in all scenario analyses conducted that influence QALY estimates (all analysis except scenarios relating to RDI estimates) as presented in Appendix A, the severity modifier remains 1.7 vs regorafenib and trifluridine-tipiracil, demonstrating the robustness of the severity modifier estimates to changing assumptions.

Table 20: Summary of updated QALY shortfall analysis, updated base case

Expected total QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute (proportional) QALY shortfall
11.16	Regorafenib: [redacted] Trifluridine-tipiracil: [redacted]	[redacted] [redacted]

Abbreviations: QALY, quality-adjusted life year.

Appendix C

Model Fits; All functions of time

Table 21: Model fits – PFS; FE

P1	P2	Dbar	Dhat	DIC	pD
-3	-3	1209	1176	1241	32.59
-3	-2	1236	1203	1269	33.13
-3	-1	1280	1247	1313	32.83
-3	-0.5	1311	1278	1344	32.83
-3	0	1348	1316	1381	32.73
-3	0.5	1391	1359	1424	32.68
-3	1	1437	1405	1470	32.71
-3	2	1526	1493	1558	32.27
-3	3	1591	1560	1623	31.78
-3	FirstOrder	1692	1671	1714	21.76
-2	-2	1271	1238	1303	32.8
-2	-1	1329	1296	1362	33.07
-2	-0.5	1370	1337	1403	33.03
-2	0	1420	1387	1453	33.07
-2	0.5	1476	1443	1509	33.01
-2	1	1535	1502	1568	32.73
-2	2	1649	1616	1682	33.08
-2	3	1735	1703	1767	32.42
-2	FirstOrder	1871	1850	1893	21.95
-1	-1	1412	1379	1445	32.84
-1	-0.5	1470	1437	1503	32.71
-1	0	1538	1506	1571	32.7
-1	0.5	1615	1582	1648	32.74
-1	1	1695	1662	1728	33.15
-1	2	1845	1813	1878	32.16
-1	3	1962	1930	1994	31.95
-1	FirstOrder	2166	2144	2188	22.06
-0.5	-0.5	1539	1506	1571	32.73
-0.5	0	1619	1586	1653	33.13
-0.5	0.5	1708	1675	1740	32.84
-0.5	1	1799	1766	1832	32.76
-0.5	2	1972	1939	2005	33.17
-0.5	3	2105	2073	2138	32.4
-0.5	FirstOrder	2350	2328	2372	21.87
0	0	1712	1679	1744	32.73
0	0.5	1812	1780	1845	32.83
0	1	1915	1883	1948	32.72
0	2	2107	2074	2140	32.76

Company response to the Committee's requests following ACM2

P1	P2	Dbar	Dhat	DIC	pD
0	3	2255	2223	2287	32.37
0	FirstOrder	2536	2514	2558	21.88
0.5	0.5	1924	1892	1957	32.5
0.5	1	2037	2005	2070	32.92
0.5	2	2244	2211	2276	32.21
0.5	3	2403	2372	2434	31.12
0.5	FirstOrder	2697	2675	2719	21.92
1	1	2159	2126	2192	33.03
1	2	2373	2341	2405	31.85
1	3	2532	2499	2564	32.39
1	FirstOrder	2810	2788	2832	21.98
2	2	2587	2555	2619	32.34
2	3	2722	2690	2754	32.04
2	FirstOrder	2900	2878	2922	22.08
3	3	2822	2793	2852	29.55
3	FirstOrder	2915	2892	2937	22.11

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effect; pD, leverage (effective number of parameters); PFS, Progression-free survival; P1, 1st Power; P2, 2nd Power.

Table 22: Model fits – PFS; RE

P1	P2	Dbar	Dhat	DIC	pD
-3	-3	1203	1168	1239	35.6
-3	-2	1230	1194	1266	35.91
-3	-1	1274	1237	1311	37.2
-3	-0.5	1306	1270	1342	35.79
-3	0	1340	1303	1376	36.14
-3	0.5	1382	1346	1419	36.69
-3	1	1426	1390	1463	36.54
-3	2	1512	1476	1549	36.67
-3	3	1576	1541	1612	35.45
-2	-2	1265	1228	1301	36.34
-2	-1	1322	1285	1358	36.6
-2	-0.5	1363	1327	1399	35.79
-2	0	1411	1374	1449	37.27
-2	0.5	1464	1428	1499	35.46
-2	1	1523	1486	1560	37.02
-2	2	1635	1598	1672	36.89
-2	3	1720	1684	1755	35.23
-2	4	1775	1741	1808	33.61
-2	FirstOrder	1858	1832	1883	25.89
-1	-1	1405	1368	1442	36.9
-1	-0.5	1460	1426	1494	33.89

Company response to the Committee's requests following ACM2

P1	P2	Dbar	Dhat	DIC	pD
-1	0	1534	1499	1569	35.42
-1	0.5	1603	1567	1638	35.15
-1	1	1682	1646	1718	36.04
-1	2	1832	1795	1868	36.5
-1	3	1950	1914	1986	35.74
-1	FirstOrder	2155	2129	2181	25.91
-0.5	-0.5	1532	1498	1566	33.92
-0.5	0	1609	1576	1643	33.75
-0.5	0.5	1695	1661	1729	33.65
-0.5	1	1784	1750	1818	34.33
-0.5	2	1959	1923	1995	36.41
-0.5	3	2093	2057	2128	35.74
-0.5	FirstOrder	2342	2316	2368	25.79
0	0	1699	1662	1736	36.81
0	0.5	1797	1763	1832	34.46
0	1	1902	1865	1939	36.76
0	2	2094	2059	2130	35.96
0	3	2244	2209	2279	34.93
0	FirstOrder	2530	2504	2555	25.39
0.5	0.5	1910	1876	1944	33.98
0.5	1	2025	1989	2060	35.53
0.5	2	2234	2199	2269	35.4
0.5	3	2392	2357	2427	35.02
0.5	FirstOrder	2691	2666	2716	24.75
1	1	2147	2111	2184	36.68
1	2	2365	2330	2401	35.45
1	3	2525	2490	2560	35.03
1	FirstOrder	2804	2779	2829	25.15
2	2	2580	2545	2616	35.3
2	3	2716	2681	2750	34.35
2	FirstOrder	2894	2868	2919	25.51
3	3	2816	2783	2850	33.35
3	FirstOrder	2907	2881	2932	25.2

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effect; pD, leverage (effective number of parameters); PFS, Progression-free survival; P1, 1st Power; P2, 2nd Power.

Table 23: Model fits – OS; FE

P1	P2	Dbar	Dhat	DIC	pD
-3	-3	1133	1100	1165	32.38
-3	-2	1133	1101	1165	32.28
-3	-1	1140	1108	1172	32.23
-3	-0.5	1147	1115	1179	31.86

Company response to the Committee's requests following ACM2

P1	P2	Dbar	Dhat	DIC	pD
-3	0	1157	1125	1190	32.4
-3	0.5	1169	1136	1201	32.48
-3	1	1180	1148	1212	32.18
-3	2	1198	1167	1230	31.5
-3	3	1210	1180	1241	30.18
-3	FirstOrder	1229	1208	1250	21.3
-2	-2	1135	1102	1167	32.38
-2	-1	1138	1106	1171	32.2
-2	-0.5	1142	1110	1174	32.45
-2	0	1145	1113	1177	32.17
-2	0.5	1149	1117	1181	32.15
-2	1	1153	1121	1186	32.43
-2	2	1159	1126	1191	32.52
-2	3	1162	1130	1194	32.28
-2	FirstOrder	1164	1143	1186	21.78
-1	-1	1137	1105	1170	32.4
-1	-0.5	1138	1105	1170	32.78
-1	0	1137	1105	1170	32.18
-1	0.5	1139	1106	1171	32.64
-1	1	1140	1107	1173	32.57
-1	2	1143	1110	1175	32.28
-1	3	1143	1113	1174	30.22
-1	FirstOrder	1149	1127	1171	21.71
-0.5	-0.5	1137	1105	1169	32.09
-0.5	0	1139	1106	1172	32.99
-0.5	0.5	1143	1110	1175	32.55
-0.5	1	1148	1115	1180	32.62
-0.5	2	1160	1127	1193	32.93
-0.5	3	1167	1137	1198	30.26
-0.5	FirstOrder	1193	1170	1215	22.28
0	0	1145	1112	1177	32.66
0	0.5	1155	1122	1188	32.98
0	1	1168	1135	1201	33.02
0	2	1193	1161	1226	32.75
0	3	1214	1182	1246	31.76
0	FirstOrder	1272	1250	1295	22.28
0.5	0.5	1173	1140	1206	32.68
0.5	1	1196	1162	1229	33.19
0.5	2	1239	1206	1272	32.73
0.5	3	1272	1242	1302	30.17
0.5	FirstOrder	1371	1349	1392	21.69

Company response to the Committee's requests following ACM2

P1	P2	Dbar	Dhat	DIC	pD
1	1	1228	1195	1261	33.29
1	2	1289	1256	1322	32.83
1	3	1337	1303	1370	33.36
1	FirstOrder	1467	1445	1489	21.94
2	2	1377	1344	1410	32.72
2	3	1435	1406	1465	29.65
2	FirstOrder	1603	1581	1625	21.84
3	3	1504	1473	1535	30.83
3	FirstOrder	1673	1651	1694	21.36

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effect; pD, leverage (effective number of parameters); OS, overall survival; P1, 1st Power; P2, 2nd Power.

Table 24: Model fits – OS; RE

P1	P2	Dbar	Dhat	DIC	pD
-3	-3	1131	1095	1166	35.49
-3	-2	1131	1095	1166	35.69
-3	-1	1137	1102	1171	34.62
-3	-0.5	1145	1110	1180	35.02
-3	0	1155	1120	1190	35.04
-3	0.5	1167	1132	1202	34.94
-3	1	1179	1144	1214	35.15
-3	2	1198	1164	1232	34.15
-3	3	1208	1176	1240	32.08
-3	FirstOrder	1228	1205	1252	23.35
-2	-2	1133	1097	1169	35.92
-2	-1	1137	1102	1172	35.05
-2	-0.5	1139	1104	1174	34.95
-2	0	1143	1108	1178	35.1
-2	0.5	1148	1112	1184	35.62
-2	1	1150	1116	1185	34.41
-2	2	1157	1122	1192	35.06
-2	3	1161	1127	1195	34.26
-2	FirstOrder	1163	1139	1187	23.91
-1	-1	1134	1099	1170	35.55
-1	-0.5	1138	1105	1170	32.47
-1	0	1136	1102	1170	34.24
-1	0.5	1139	1104	1174	35.25
-1	1	1139	1104	1175	35.91
-1	2	1140	1106	1174	34.01
-1	3	1146	1111	1180	34.72
-1	FirstOrder	1148	1123	1172	24.49
-0.5	-0.5	1133	1100	1166	33.25

P1	P2	Dbar	Dhat	DIC	pD
-0.5	0	1134	1102	1167	32.53
-0.5	0.5	1138	1105	1172	33.14
-0.5	1	1145	1111	1179	33.94
-0.5	2	1157	1123	1192	34.77
-0.5	3	1167	1132	1202	34.95
-0.5	FirstOrder	1191	1166	1215	24.6
0	0	1143	1107	1179	36.13
0	0.5	1150	1116	1185	34.05
0	1	1166	1131	1201	35.08
0	2	1192	1157	1227	34.63
0	3	1212	1177	1246	34.63
0	FirstOrder	1270	1245	1295	24.71
0.5	0.5	1170	1137	1204	33.23
0.5	1	1193	1160	1225	32.07
0.5	2	1237	1202	1272	34.79
0.5	3	1274	1241	1308	33.33
0.5	FirstOrder	1371	1345	1396	25.3
1	1	1226	1190	1261	35.5
1	2	1287	1252	1322	34.73
1	3	1334	1300	1367	33.56
1	FirstOrder	1465	1441	1490	24.95
2	2	1375	1340	1409	34.25
2	3	1436	1401	1471	35.11
2	FirstOrder	1602	1578	1626	24.45
3	3	1505	1471	1539	34.3
3	FirstOrder	1673	1648	1697	24.55

Abbreviations: Dbar, mean deviance; Dhat, point estimate / plug-in deviance; DIC, deviance information criterion; FE, fixed-effect; pD, leverage (effective number of parameters); OS, overall survival; P1, 1st Power; P2, 2nd Power.

FP NMA model coefficients

The parameter estimates for coefficients β_0, β_1 and β_2 for these fractional polynomial models are reported in Table 25 for PFS and Table 26 for OS (Equation (1) presents the definition of a first-order model with coefficients, β_0 and β_1).

Company response to the Committee's requests following ACM2

Table 25: Functions of parameter estimates for different fractional polynomials – PFS

	FE model, 2nd order (-3, -3)		FE model, 2nd order (-3, -2)		FE model, 2nd order (-2, -2)	
	Median of posterior distribution	95% CrI	Median of posterior distribution	95% CrI	Median of posterior distribution	95% CrI
BSC						
β_{0A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Fruquintinib						
β_{0B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Regorafenib						
β_{0C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Trifluridine-tipiracil						
β_{0D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])

Abbreviations: BSC, best supportive care; CrI, credible interval; FE, fixed-effect; PFS, progression-free survival.

Table 26: Functions of parameter estimates for different fractional polynomials – OS

	FE model, 2nd order (-3, -3)		FE model, 2nd order (-3, -2)		FE model, 2nd order (-2, -2)	
	Median of posterior distribution	95% CrI	Median of posterior distribution	95% CrI	Median of posterior distribution	95% CrI
BSC						
β_{0A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2A}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Fruquintinib						
β_{0B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2B}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Regorafenib						
β_{0C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2C}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
Trifluridine-tipiracil						
β_{0D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{1D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])
β_{2D}	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])	[redacted]	([redacted], [redacted])

Abbreviations: BSC, best supportive care; CrI, credible interval; FE, fixed-effect; OS, overall survival.

Company response to the Committee's requests following ACM2

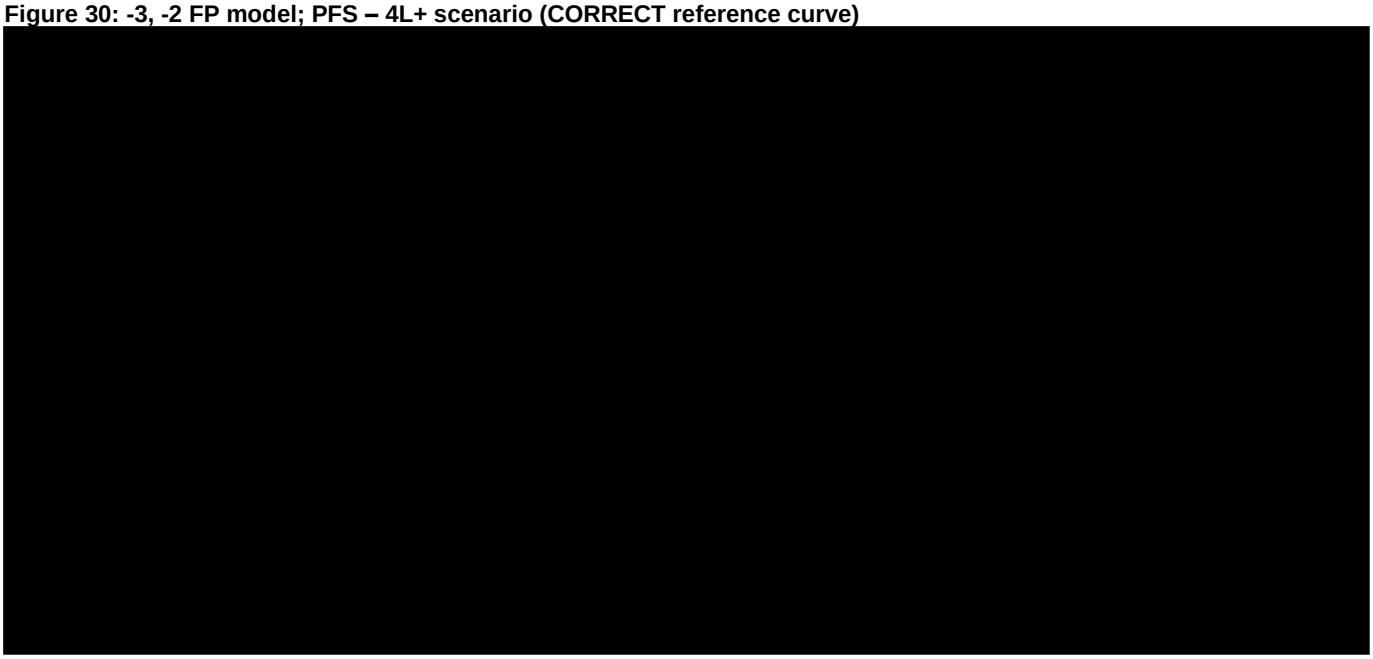
Model Selection Assessment

Additional plots and data used to inform the model choice assessment are provided below.

Figure 29: -3,-2 FP model; PFS – 3L+ base case

Abbreviations: 3L+, third-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

Figure 30: -3, -2 FP model; PFS – 4L+ scenario (CORRECT reference curve)



Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

Company response to the Committee's requests following ACM2

Figure 31: -3, -2 FP model; PFS – 4L+ scenario (FRESCO-2 reference curve)

Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

.

Figure 32: -2,-2 FP model; PFS – 3L+ base case

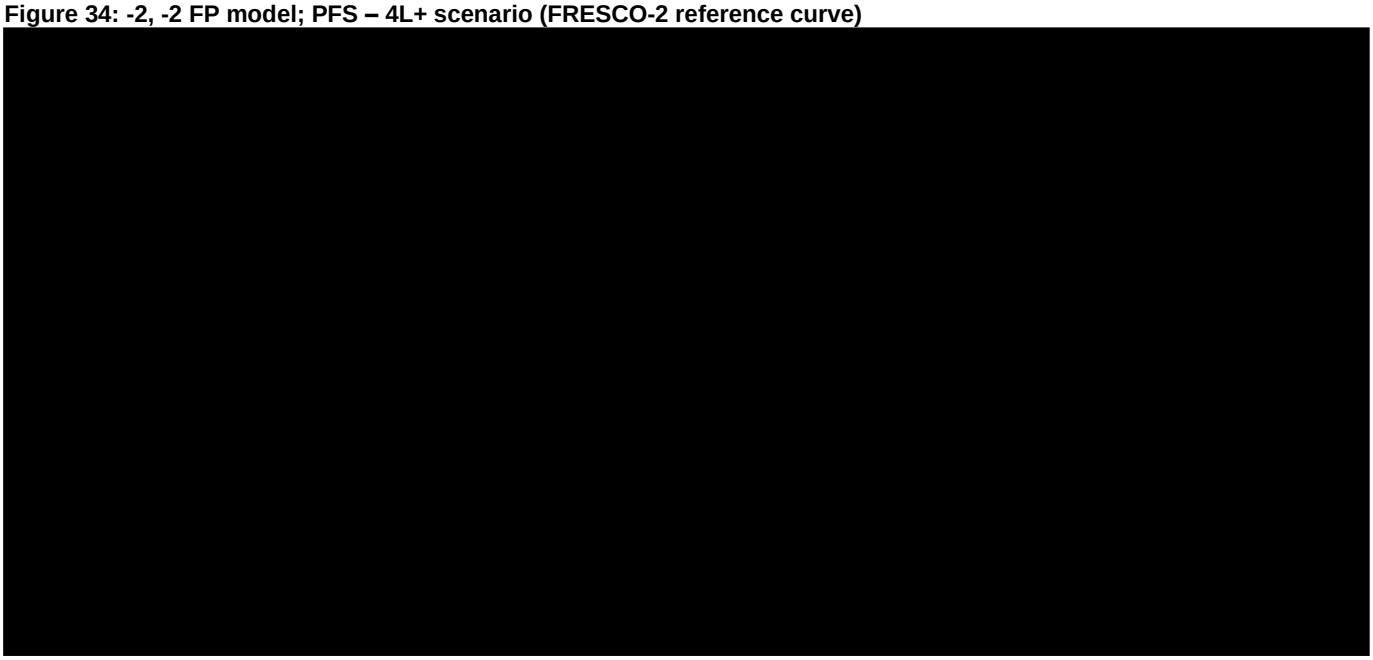
Abbreviations: 3L+, third-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

Company response to the Committee's requests following ACM2

Figure 33: -2, -2 FP model; PFS – 4L+ scenario (CORRECT reference curve)

Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

Figure 34: -2, -2 FP model; PFS – 4L+ scenario (FRESCO-2 reference curve)



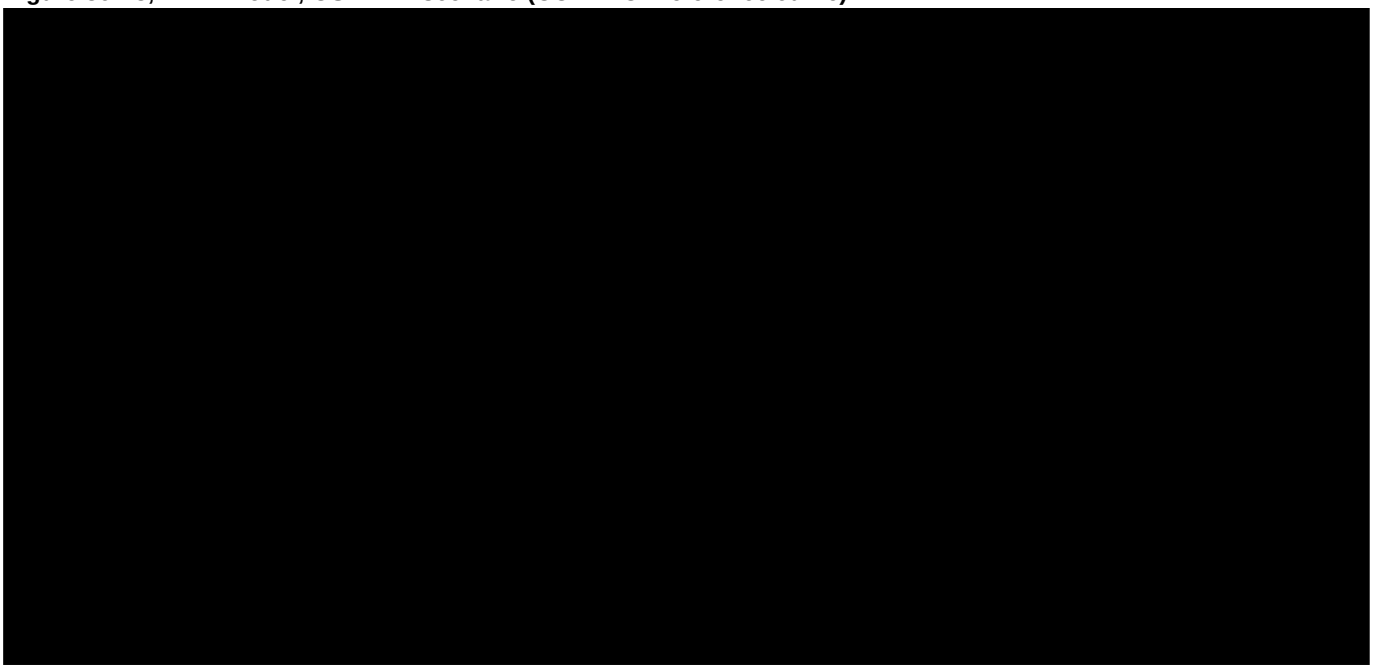
Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; PFS, progression-free survival.

Company response to the Committee's requests following ACM2

Figure 35: -3,-2 FP model; OS – 3L+ base case

Abbreviations: 3L+, third-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Figure 36: -3, -2 FP model; OS – 4L+ scenario (CORRECT reference curve)



Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Company response to the Committee's requests following ACM2

Figure 37: -3, -2 FP model; OS – 4L+ scenario (FRESCO-2 reference curve)

Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Figure 38: -2,-2 FP model; OS – 3L+ base case

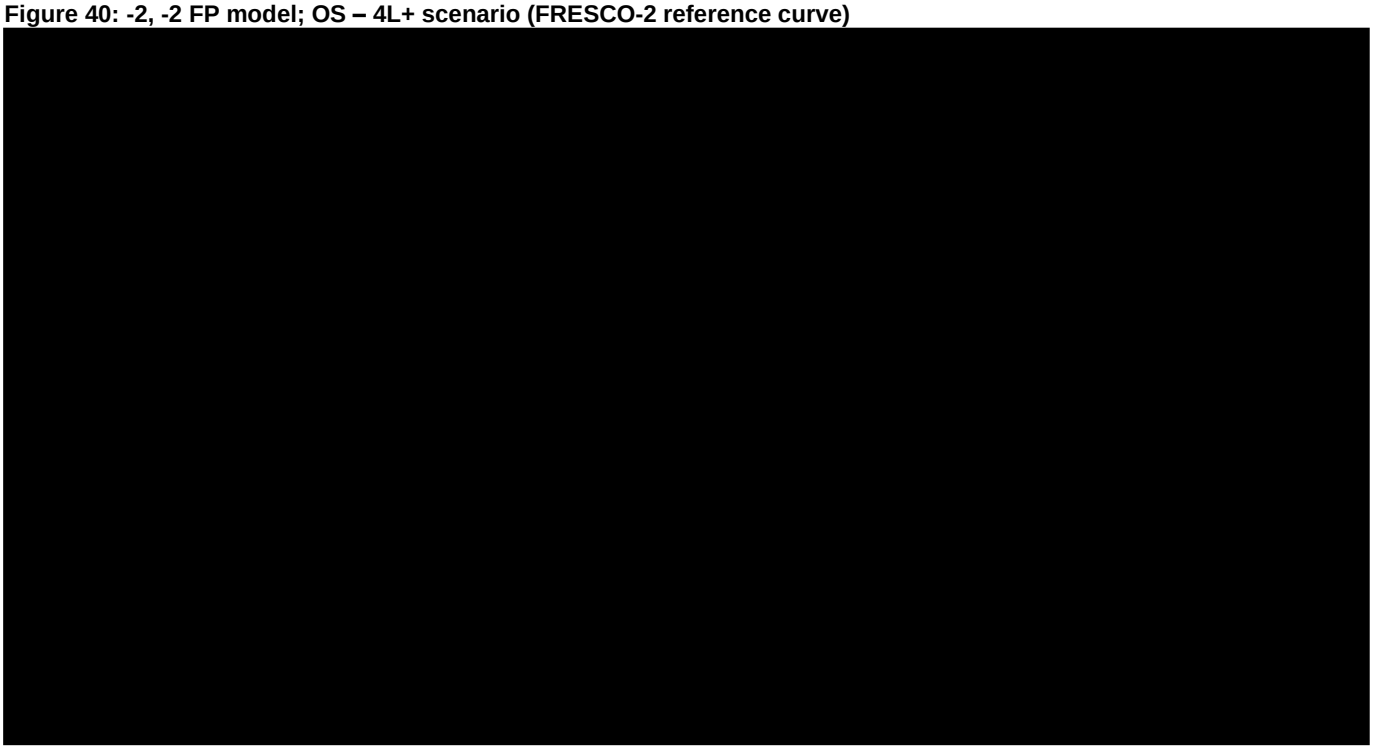
Abbreviations: 3L+, third-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Company response to the Committee's requests following ACM2

Figure 39: -2, -2 FP model; OS – 4L+ scenario (CORRECT reference curve)

Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Figure 40: -2, -2 FP model; OS – 4L+ scenario (FRESCO-2 reference curve)



Abbreviations: 4L+, fourth-line plus; BSC, best supportive care; FP, fractional polynomial; OS, overall survival.

Company response to the Committee's requests following ACM2

Table 27: Comparison of median PFS estimates across FP models and scenarios

Approach	P1	P2	Fruquintinib median PFS, months	Regorafenib median PFS, months	Trifluridine-tipiracil median PFS, months	BSC median PFS, months
Committee preferred assumptions (hazard ratio applied to pooled RECOURSE and Yoshino curve – 3L+ **base case**)	-3	-3	[redacted]	2.53	2.53	NA
	-3	-2	[redacted]	2.53	2.53	NA
	-2	-2	[redacted]	2.53	2.53	NA
Committee preferred assumptions ((hazard ratio applied to digitised CORRECT curve – 4L+ **scenario** analysis)	-3	-3	[redacted]	2.53	NA	1.38
	-3	-2	[redacted]	2.53	NA	1.38
	-2	-2	[redacted]	2.53	NA	1.38
Scenario analysis 4L+ - hazard ratio applied to FRESCO-2 reference curve	-3	-3	[redacted]	2.99	N/A	1.84
	-3	-2	[redacted]	2.99	NA	1.84
	-2	-2	[redacted]	2.99	N/A	1.84

Abbreviations: BSC, best supportive care; FP, fractional polynomial; NA, not applicable; PFS, progression-free survival.

Table 28: Comparison of median OS across FP models (no capping)

Approach	P1	P2	Fruquintinib median OS, months	Regorafenib median OS, months	Trifluridine-tipiracil median OS, months	BSC median OS, months
Committee preferred assumptions (hazard ratio applied to SACT reference curve – 3L+ **base case**)	-3	-3	[redacted]	6.90	7.13	NA
	-3	-2	[redacted]	6.90	7.13	NA
	-2	-2	[redacted]	6.90	7.13	NA
Committee preferred assumptions ((hazard ratio applied to digitised CORRECT reference curve – 4L+ **scenario**)	-3	-3	[redacted]	6.44	NA	5.06
	-3	-2	[redacted]	6.44	NA	5.06
	-2	-2	[redacted]	6.44	NA	5.06
Scenario analysis 4L+ – hazard ratio applied to FRESCO-2 reference curve	-3	-3	[redacted]	6.44	N/A	4.37
	-3	-2	[redacted]	6.44	NA	4.37
	-2	-2	[redacted]	6.44	N/A	4.37

Abbreviations: BSC, best supportive care; FP, fractional polynomial; OS, overall survival; NA, not applicable; SACT, systemic anti-cancer therapy.

Company response to the Committee's requests following ACM2

Table 29: Comparison of median OS across FP models (capping)

Approach	P1	P2	Fruquintinib median OS, months	Regorafenib median OS, months	Trifluridine-tipiracil median OS, months	BSC median OS, months
Committee preferred assumptions (hazard ratio applied to SACT reference curve – 3L+ **base case**)	-3	-3	[redacted]	6.90	7.13	NA
	-3	-2	[redacted]	6.90	7.13	NA
	-2	-2	[redacted]	6.90	7.13	NA
Committee preferred assumptions ((hazard ratio applied to digitised CORRECT reference curve – 4L+ **scenario**)	-3	-3	[redacted]	6.44	NA	5.06
	-3	-2	[redacted]	6.44	NA	5.06
	-2	-2	[redacted]	6.44	NA	5.06
Scenario analysis 4L+ – hazard ratio applied to FRESCO-2 reference curve	-3	-3	[redacted]	6.21	N/A	4.37
	-3	-2	[redacted]	6.21	NA	4.37
	-2	-2	[redacted]	6.21	N/A	4.37

Abbreviations: BSC, best supportive care; FP, fractional polynomial; OS, overall survival; NA, not applicable; SACT, systemic anti-cancer therapy.

Hazards over time; RE

Figure 41: OS hazards over time, RE (-2, -2)

Abbreviations: BSC, Best Supportive care; Fruq, fruquintinib; OS, Overall survival; RE, random effect.

Company response to the Committee's requests following ACM2

Figure 42: OS hazards over time, RE (-3, -3)

Abbreviations: BSC, Best Supportive care; Fruq, fruquintinib; OS, Overall survival; RE, random effect.

Figure 43: PFS hazards over time, RE (-2, -2)

Abbreviations: BSC, Best Supportive care; Fruq, fruquintinib; PFS, Progression-free survival; RE, random effect.

Company response to the Committee's requests following ACM2

Figure 44: PFS hazards over time, RE (-3, -3)

Abbreviations: BSC, Best Supportive care; Fruq, fruquintinib; PFS, Progression-free survival; RE, random effect.

Hazard ratios over time; -3, -3

Table 30: PFS hazard ratios over time in the model; -3, - 3, 3L+ base case (vs trifluridine-tipiracil) – no capping

Comparator (vs trifluridine-tipiracil)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, Best supportive care; PFS, Progression-free survival.

Company response to the Committee's requests following ACM2

Table 31: PFS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs regorafenib CORRECT) – no capping

Comparator (vs regorafenib)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, Best supportive care; PFS, Progression-free survival.

Table 32: PFS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs fruquintinib FRESCO-2) – no capping

Comparator (vs fruquintinib)	Timepoint (Months)	Hazard ratio
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, best supportive care; PFS, progression-free survival.

Table 33: OS hazard ratios over time in the model; -3, - 3, 3L+ (vs trifluridine-tipiracil) – no capping

Comparator (vs trifluridine-tipiracil)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]

Company response to the Committee's requests following ACM2

Comparator (vs trifluridine-tipiracil)	Timepoint (Months)	Hazard ratio
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, best supportive care; OS, overall survival.

Table 34: OS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs regorafenib CORRECT) – no capping

Comparator (vs regorafenib)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, best supportive care; PS, overall survival.

Table 35: OS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs fruquintinib FRESCO-2) – no capping

Comparator (vs fruquintinib)	Timepoint (Months)	Hazard ratio
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Company response to the Committee's requests following ACM2

Comparator (vs fruquintinib)	Timepoint (Months)	Hazard ratio
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]

Abbreviations: BSC, best supportive care; OS, overall survival.

Fruquintinib for previously treated metastatic colorectal cancer [ID6274]

ADDITIONAL EAG CRITIQUE POST ACM2

CONFIDENTIAL

Produced by **Aberdeen HTA Group**

Authors: Dwayne Boyers[1]
David Cooper[2]

1 Health Economics Research Unit (HERU), University of Aberdeen, UK
2 Aberdeen Centre for Evaluation (ACE), University of Aberdeen, UK

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Correspondence to: Dwayne Boyers
Senior Research Fellow
Health Economics Research Unit
University of Aberdeen, UK
Email: d.boyers@abdn.ac.uk

Strictly confidential: Contains [redacted] and [redacted] information

1 Overview

This document provides a critique of the company's response to additional NICE committee work requests following the second appraisal committee meeting for the NICE technology appraisal of Fruquintinib for previously treated metastatic colorectal cancer [ID6274]. The company provided several updates to their base case analysis and explored additional scenarios in line with NICE committee preferences and requests for additional information following ACM2.

In addition to the updated base case analysis, the company have also increased their simple PAS discount to a [redacted] reduction from the NHS list price, compared to a [redacted] reduction in the original submission and [redacted] reduction at draft guidance. The current version of the economic model incorporates the latest reduction, with discounted fruquintinib prices of [redacted] All cost-effectiveness results provided in this document apply the most recent confidential PAS discounted prices for fruquintinib.

Commercial in confidence CMU and cPAS prices for regorafenib, trifluridine-tipiracil and other concomitant and post-progression treatments used in the economic model are provided in a confidential appendix to this document. Full details of all ICERs provided in the company's response, with confidential comparator prices applied can be found in Section 3 of this document. [redacted]

2. Company updates to the base-case analysis:

The updated base case analysis applied HRs from a fractional polynomial NMA

At ACM2, NICE requested that the company conduct further analyses to confirm whether proportional hazards (PH) hold and if not to update the network meta-analysis (NMA) analyses using fractional polynomials.

The Company first present tests of the interaction between treatment and time and treatment and log-time for the comparison of fruquintinib and BSC using the pooled FRESCO and FRECO-2 data for PFS and OS. The Company reiterate their statement from the previous committee meeting that these tests are not explicitly recommended in NICE DSU methods guidance when testing whether the proportional hazards assumption holds. The Company

recognises however that the conclusion of the tests on the interaction term suggests the proportional hazard assumption might not hold for PFS or OS. To explore the impact of this uncertainty on results, as requested by the Committee, the Company present fractional polynomial NMA results for all treatments for both OS and PFS. The Company highlight issues in the method with "implausible crossing of curves", leading to higher QALYs for regorafenib compared to fruquintinib, which lacks clinical plausibility. The company also note that the model estimates underestimate clinical expert opinion. The Company references other NICE submissions where similar issues have been observed. The company apply HRs from the fractional polynomial NMA in their updated base case analysis, with additional capping to ensure that the hazard curves for fruquintinib and comparators do not cross.

The EAG have reviewed the methods used by the Company and these are consistent with what have been applied in other technology appraisals and use the methods recommended in NICE DSU TSD21. The EAG agrees with the Company that capping of the hazards where the curves cross when this is considered clinically implausible does produce OS and PFS results which are similar to those of the relevant RCTs. This leads the EAG to agree with the view of the EAG in TA739 that the fractional polynomial method may not be suitable if the only way to obtain plausible results is to cap the hazard ratios. This point is also made by the Company in their summary. The Company were also required to use estimation methods to obtain the required data for all comparisons. TA858 and TA530 also reviewed fractional polynomials methods and encountered several uncertainties. It is therefore the EAG's opinion that in response to the various uncertainties with the fractional polynomial method that the proportional hazard assumption method is more suitable for decision making.

If the FP NMA results are to be used in the economic modelling, the EAG agree with the company that capping the hazards is appropriate to prevent implausible outcomes that are inconsistent with clinical expectations for the relevant treatment benefit of fruquintinib vs. comparators. The analyses provided by the company are useful in terms of assessing the magnitude of uncertainty surrounding the decision to use a standard or FP NMA on estimates of the ICER. When the FP NMA hazards are capped, the EAG note that the results provided by the standard NMA and FP NMA are very similar, leading to similar estimates of the ICER. The decision on whether to apply standard or FP NMA results in the economic model is therefore not a major determinant of cost-effectiveness for this appraisal.

The tables below present comparisons of the NMA analysis hazard ratios under the proportional hazards assumption and the fractional polynomial methods. Information from Section B.2.9.5.1 table 19 (p86) and Section B.2.9.5.2 table 21 (p88) of the Company submission and then the indicated tables from appendix C of the Company's response document have been used to generate these tables.

Table 1: PFS hazard ratios over time in the model; -3, - 3, 3L+ base case (vs trifluridine-tipiracil) – no capping

Comparator (vs trifluridine-tipiracil)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		0.67
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.01

Table 2: PFS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs regorafenib CORRECT) – no capping

Comparator (vs regorafenib)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		0.66
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		2.22

Table 3: PFS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs fruquintinib FRESCO-2) – no capping

Comparator (vs fruquintinib)	Timepoint (Months)	Hazard ratio
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.515
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		3.333

Table 4: OS hazard ratios over time in the model; -3, - 3, 3L+ (vs trifluridine-tipiracil) – no capping

Comparator (vs trifluridine-tipiracil)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		0.95
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.02

Table 5: OS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs regorafenib CORRECT) – no capping

Comparator (vs regorafenib)	Timepoint (Months)	Hazard ratio
Fruquintinib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		0.93
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.408

Table 6: OS hazard ratios over time in the model; -3, - 3, 4L+ scenario (vs fruquintinib FRESCO-2) – no capping

Comparator (vs fruquintinib)	Timepoint (Months)	Hazard ratio
Regorafenib	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.075
BSC	1	[redacted]
	2	[redacted]
	3	[redacted]
	4	[redacted]
	5	[redacted]
	6	[redacted]
	12	[redacted]
	24	[redacted]
	36	[redacted]
NMA analysis HR		1.515

Health state utility values have been updated to apply utilities obtained from a pooled fixed effects meta-analysis in the 3L+ setting, with FRESCO-2 utilities applied in the 4L+ setting

For the 3L+ setting, the company provided an updated analysis of HSUVs, obtained from a fixed effects meta-analysis across several mCRC trials, namely FRESCO-2, CONCUR / CORRECT pooled, and SUNLIGHT for application in the economic model. A scenario analysis was provided excluding SUNLIGHT data, noting EAG concerns that these may be an over-estimate. The following health state utility values were therefore considered in the company's revised analyses, detailed in Table 7 below.

Table 7: Alternative health state utility values for application in the economic model

Trial	Progression-free: mean	Progressed: mean
FRESCO-2 (Company base case 4L+)	0.71	0.65
CONCUR/CORRECT pooled	0.72	0.59
SUNLIGHT	0.76	0.68
Fixed effects meta-analysis (all studies) – Company revised base case 3L+	0.72	0.64
Fixed effects meta-analysis (excluding SUNLIGHT)	0.72	0.63

The EAG are satisfied that the company's updated HSUVs are correctly derived and applied appropriately in the updated economic model. The EAG also considers it appropriate to apply the pooled HSUVs for the 3L+ setting with FRESCO-2 utilities applied in the 4L+ setting.

Relative dose intensity for fruquintinib, regorafenib and trifluridine-tipiracil

The company updated analysis applied RDIs for fruquintinib, regorafenib and trifluridine-tipiracil from the respective clinical trials as opposed to the original submission which assumed equal RDIs across all treatments.

The EAG are satisfied that the RDIs have been appropriately incorporated into the revised economic model. The company's revised base case is now aligned with the EAG preferred base case and NICE preferred assumptions from ACM2.

Mean starting age of the modelled cohort

The company base case analysis has been updated to include the mean starting age for 3L+ and 4L+ treatments, sourced from the SACT dataset. Specifically, the revised starting age in the model has been updated to 64.3 in the 3L+ setting (mean starting age in SACT for patients receiving trifluridine-tipiracil) and to 64.7 in the 4L+ setting (mean starting age in SACT for patients receiving regorafenib).

The EAG acknowledges that new treatments in the pathway (e.g. trifluridine-tipiracil + bevacizumab) may alter start ages on fruquintinib in UK clinical practice going forward. However, the EAG consider the SACT data to be the most representative of current UK clinical practice and are therefore appropriate for decision making.

4L+ setting

As per the committee's request, the company have provided a range of analyses to explore the cost-effectiveness of fruquintinib compared to both regorafenib and BSC at 4th line + treatment. To do this, the company have applied FP NMA HRs to a) the regorafenib reference curve from CORRECT as per committee's request and b) to the fruquintinib curve from FRESCO -2. Utilities for the 4L setting are updated to apply FRESCO-2 and the mean starting age from the SACT data.

The EAG are satisfied that the company's approach to modelling 4L+ treatment is reasonable. The company raise valid points about the concerns with applying HRs to the CORRECT regorafenib reference curve in the 4L+ setting and therefore also provide analyses vs. the Fruquintinib curve from FRESCO-2. The EAG consider both approaches to be plausible and note that the impact on the ICER is small.

Severity modifier

The company have updated their severity modifier calculations using the committee preferred base case assumptions and preferences. Results of the severity modifier calculations (applying FP NMAs, fixed-effects meta-analysis utility values across all studies, starting age from SACT) are presented in Table 11 (3L+) and Table 12 (4L+). Severity weighting calculations across scenario analyses underpinning the committee preferred base case are provided in Tables 14 (3L+) and 16 (4L+) respectively.

The EAG are satisfied that in all scenarios the severity modifier calculations produce a severity weighting of x1.7 based on proportional QALY shortfall.

3. Cost-effectiveness results accounting for [redacted] prices

Tables 8 and 9 below reproduce Tables 13 and 15 from the company's response to committee requests following ACM2, with confidential cPAS prices applied to comparators and other treatments included in the economic model. [redacted]

Table 8: Updated scenario analyses, deterministic, 3L+ population, cumulative, severity weighting = x1.7 (re-produces Table 13 of the company response to committee questions following ACM2)

Scenario	ICER versus Regorafenib			ICER versus tri-tip			ICER versus BSC		
	Inc. Cost	Inc. QALY	ICER	Inc. Cost	Inc. QALY	ICER	Inc. Cost	Inc. QALY	ICER
Company preferred base case ACM2	[redacted]								
+ updated PAS									
+ SACT starting age									
+ FP NMA, with hazard capping									
+ treatment specific RDI									
+ utilities from pooled FE meta-analysis **(Updated base case post ACM2)**									

Table 9: Updated scenario analyses, deterministic, 4L+ population, cumulative, severity weighting = x1.7 (re-produces Table 15 of the company response to committee questions following ACM2)

Scenario	ICER versus Regorafenib			ICER versus tri-tip			ICER versus BSC		
	Inc. Cost	Inc. QALY	ICER	Inc. Cost	Inc. QALY	ICER	Inc. Cost	Inc. QALY	ICER
Company preferred base case ACM2 (4L+)	[redacted]								
+ updated PAS									
+ SACT starting age									
+ FP NMA, with hazard capping									
+ treatment specific RDI									
+ utilities from FRESCO-2 **(Updated base case 4L+ post ACM2)**									