Single Technology Appraisal

Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Contents:

The following documents are made available to stakeholders:

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

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Consultation on the draft guidance document – deadline for comments end of day on **27 June 2024**.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):	Servier Laboratories 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.	None
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[Insert name]

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.
1 Overall survival extrapolation	In Section 3.8 of the draft guidance, it states that the committee considered the company's log-logistic or EAG's generalised gamma could be plausible but both were uncertain. They concluded that additional analyses in which a hazard ratio from SUNLIGHT is applied to long-term survival data from UK clinical practice were needed to help resolve this uncertainty. Servier have aimed to address this uncertainty through assessing plausibility of the log-logistic and generalised gamma curves and also through the use of real-world data sources to help understand longer-term survival data from UK practice. **<u>Log-logistic versus generalised gamma</u>** For trifluridine-tipiracil monotherapy, the log-logistic and generalised gamma extrapolations provide similar fits to the SUNLIGHT data, as well as similar long-term estimates and statistical fits. Therefore, the impact on the ICER is mainly affected by the resulting curve chosen for trifluridine-tipiracil plus bevacizumab (which is less mature at the data-cut off due

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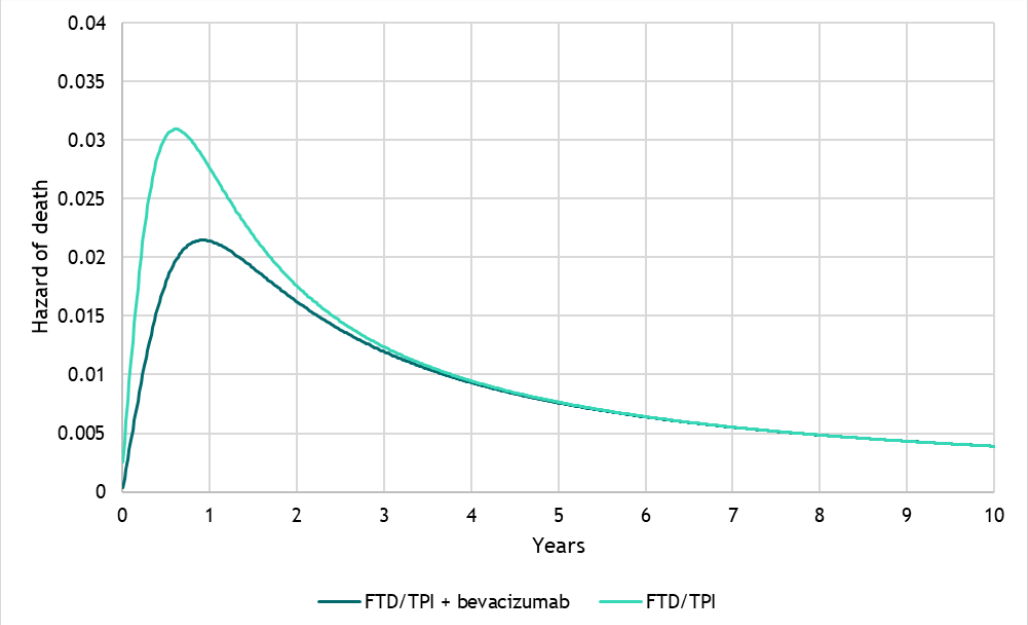
to the improvement in survival versus the monotherapy arm). The visual fits to the SUNLIGHT data are similar, however the long-term estimates differ. Log-logistic projects 2.9% being alive at 5 -years whereas generalised gamma projects 0.2%. Servier defended their base case choice in the log-logistic curve based on clinical opinion received during the submission process as well as concerns that the generalised gamma curve cross with the monotherapy arm suggesting no survival benefit at 3 years. Log-logistic is also consistent with the accepted curve for trifluridine monotherapy in TA405.[1]

In examining the hazard profiles of the log-logistic and generalised gamma curves, the log-logistic curves are much more plausible. For log-logistic, the hazard of death for trifluridine-tipiracil plus bevacizumab is lower initially, then after ~1 year, the curves gradually trend towards the same hazard, being nearly equivalent by 3 years and the same approximate hazard of death from 4 years (**Figure *1***). The generalised gamma curves, show an initial benefit for trifluridine-tipiracil plus bevacizumab for the first 18 months, then the hazard of death crosses with the monotherapy hazard and projects a higher hazard from 18 months (**Figure *2***). This appears extremely implausible based on the results of the SUNLIGHT trial showing a significant benefit of OS. As such, this further demonstrates the inappropriateness of the generalised gamma curves being used to inform OS extrapolations (where the hazard of death is much worse in the long-term for the trifluridine-tipiracil plus bevacizumab arm, and the resulting survival extrapolations cross).

Figure 1: Hazard of death – SUNLIGHT – log-logistic



Key: FTD/TPI, trifluridine-tipiracil

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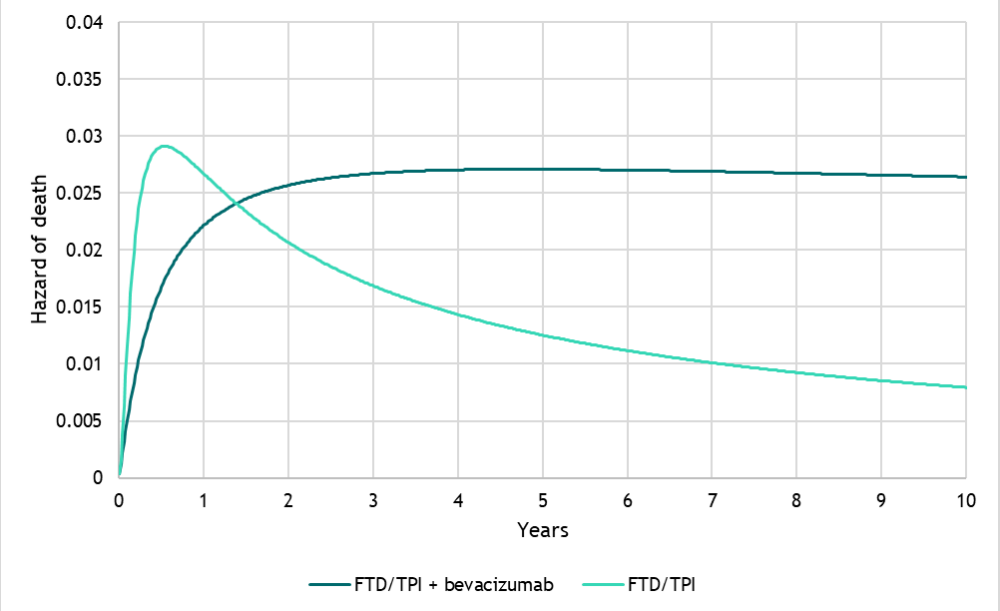
Figure 2: Hazard of death – SUNLIGHT – generalised gamma



Key: FTD/TPI, trifluridine-tipiracil

Additionally, log-logistic was chosen for the base case survival extrapolations in TA405[1] to inform of trifluridine-tipiracil monotherapy from the RECOURSE trial therefore showing consistency with our base case choice and approach.

UK clinical practice

Servier found three UK real-world evidence sources showing survival of patients who received trifluridine-tipiracil monotherapy in UK clinical practice.

1. Tong et al, 2021[2] published long-term real-world outcomes of patients receiving trifluridine-tipiracil in a single cancer centre in the UK between 2016-2017 all of which had a minimum follow-up of 2 years. 56 patients were included in the review with median follow-up of 6 months. Median overall survival was 5.8 months (range 1-28).

2. Wadd et al, 2022[3] published real-world outcomes of patients receiving different treatments in colorectal cancer (including trifluridine-tipiracil) using local SACT data from three NHS trusts. 77 patients in the dataset received trifluridine-tipiracil with median follow-u of 20 months and median survival of 6.7 months (95% CI 5.4-9.0 months).

3. Audit data was provided to Servier [redacted]. Patient-level data of patients receiving trifluridine-tipiracil was provided with a median age of [redacted] female. These data were combined resulting in [redacted] patients with median survival [redacted]

4. SACT data was provided to Servier from NHS England and contains survival data for over 6,000 mCRC patients treated with trifluridine-tipiracil monotherapy in England. Median survival was 7.1 months (95% CI: 6.8-7.3 months).

5. The PROMETCO study is collecting real-world data on metastatic colorectal cancer (mCRC) patients with two progressions[4]. This international, prospective, longitudinal,

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observational cohort study is collecting data on mCRC patients with two disease progressions since diagnosis and receiving subsequent treatment. Prometco data was provided to Servier from [redacted] patients that were treated with trifluridine-tipiracil monotherapy in 3rd or 4th line mCRC. Mean age was [redacted] years old with [redacted] female and [redacted] male[5]

The different data sources show very similar outcomes to not just one another but also to the trifluridine-tipiracil monotherapy data from the SUNLIGHT trial (**Figure *3***).

Figure 3: Trifluridine-tipiracil overall survival (SUNLIGHT vs real-world datasets)

Patient level data was available for the audit data and SACT data. The Wadd et al, and Tong et al data sources were individually digitised, and pseudo patient-level data created using the Guyot algorithm (for published Kaplan-Meiers) for each study. Parametric survival models were fitted to the data and incorporated into the cost-effectiveness model as options to model the trifluridine-tipiracil OS. For all the data sources, the curves projected similar long-term outcomes and similar statistical fits, therefore, to be consistent with the base case, log-logistic was selected for all scenarios. Further details of the parametric models are presented in Appendix 2. To inform the OS efficacy of trifluridine-tipiracil plus bevacizumab, regorafenib and BSC, the NMA HR's were applied to the trifluridine-tipiracil monotherapy curve:

- Vs trifluridine-tipiracil plus bevacizumab: OS: 1.69 (95% CI: 1.27 – 2.33),
- Vs regorafenib: OS: 1.01 (95% CI: 0.73 – 1.45))
- Vs BSC: OS: 0.70 (95% CI: 0.56 – 0.86)

The resulting OS outcomes are presented in ***Figure 4*** - **Figure *8*** including trifluridine-tipiracil monotherapy from SUNLIGHT. Results of these scenarios are presented in Table 1. Given the committee preference to use trifluridine-tipiracil monotherapy as the base curve, with other treatments informed by HRs from the NMA, Servier's revised base case includes this option

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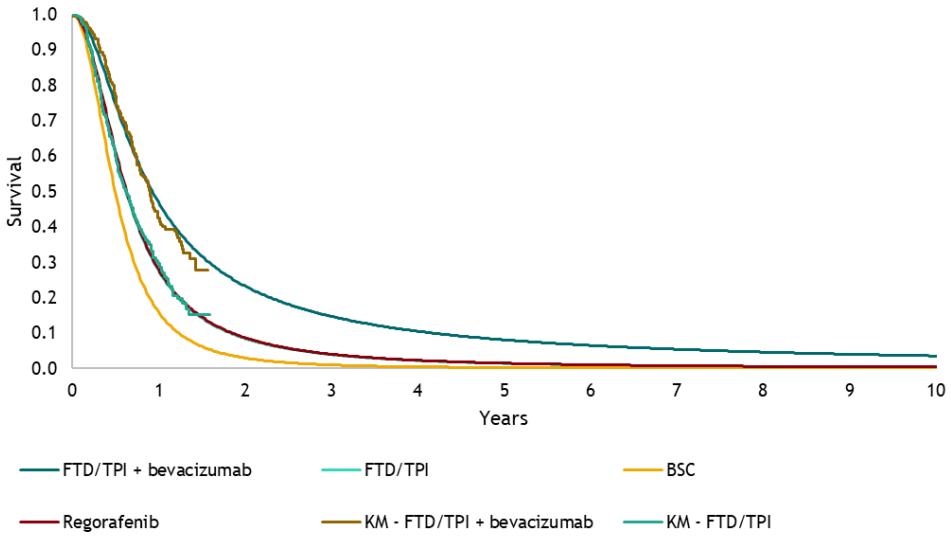
using the SUNLIGHT efficacy to model trifluridine-tipiracil monotherapy as this aligns with other inputs in the model. For consistency the PFS HRs from the NMA are also applied to the trifluridine-tipiracil monotherapy PFS.

Figure 4: Overall survival – HRs applied to trifluridine-tipiracil (SUNLIGHT)



Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier

Figure 5: Overall survival – HRs applied to trifluridine-tipiracil (Audit data)

[redacted]

Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier

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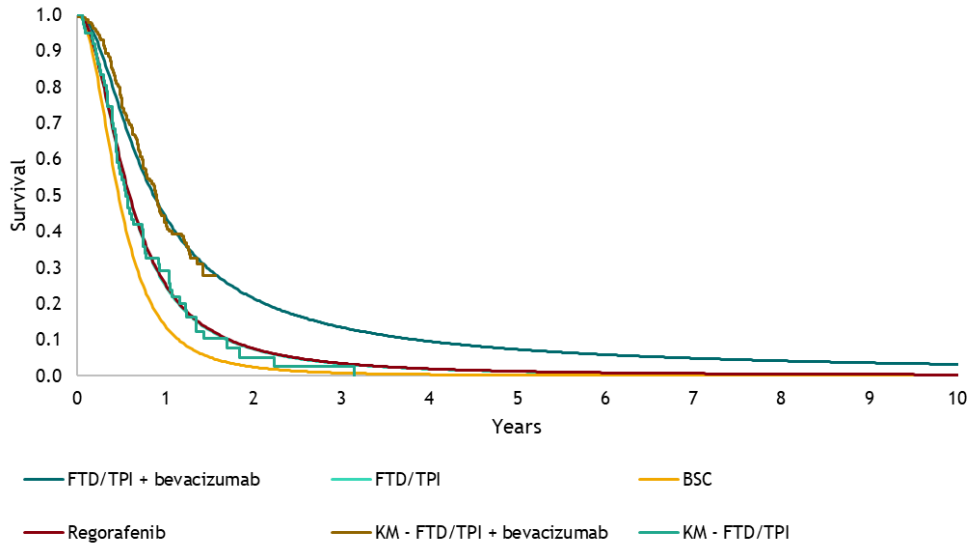
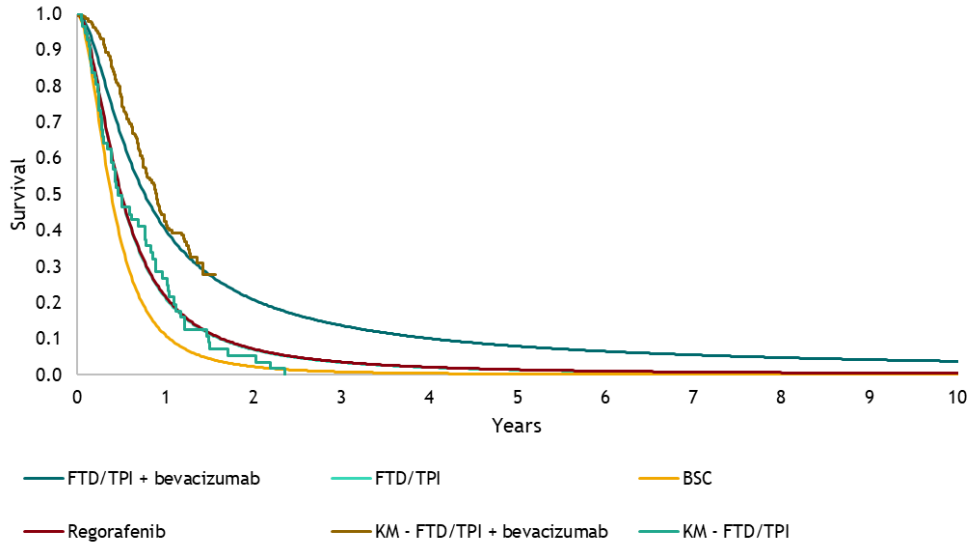
Figure 6: Overall survival – HRs applied to trifluridine-tipiracil (Wadd et al, 2022)



Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier

Figure 7: Overall survival – HRs applied to trifluridine-tipiracil (Tong et al, 2021)



Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier

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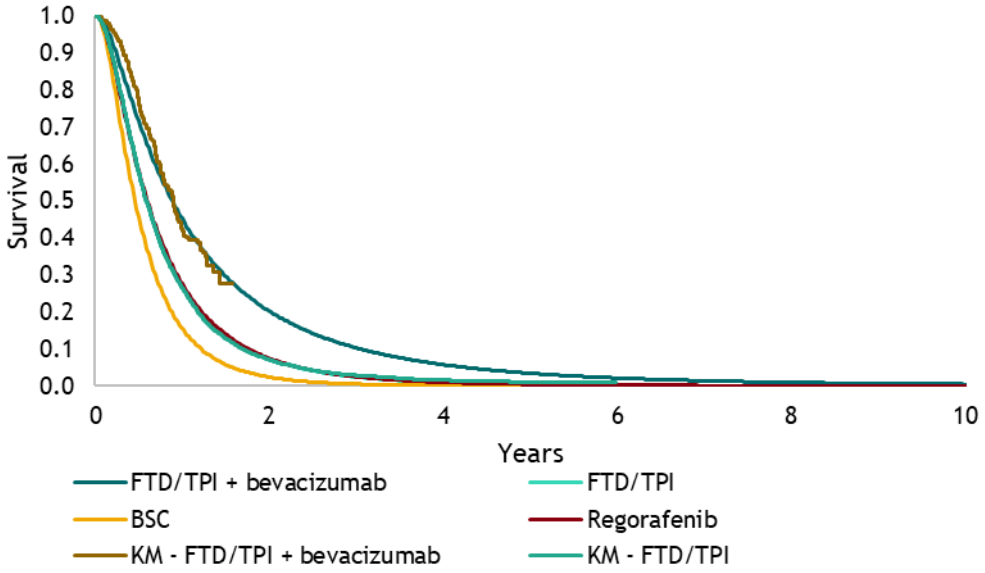
	Figure 8: Overall survival – HRs applied to trifluridine-tipiracil (SACT data)  Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier In all instances, the data shows that even with the use of external data to inform the trifluridine-tipiracil monotherapy arm, the projected survival of the trifluridine-tipiracil plus bevacizumab arm is closely aligned with that observed in the SUNLIGHT study. The new approach has been included in the revised cost-effectiveness model with gives the option to select which source to use to inform the trifluridine-tipiracil monotherapy arm.
2 Regorafenib overall and progression-free survival	In Section 3.9 of the draft guidance, the committee stated they preferred Servier's approach to modelling regorafenib's OS and PFS using the NMA. However, they considered it to be more appropriate to use trifluridine-tipiracil monotherapy as the reference curve instead of trifluridine-tipiracil plus bevacizumab. Servier has amended this in the cost-effectiveness model to allow an option to model regorafenib's OS and PFS using the NMA HR applied to the trifluridine-tipiracil monotherapy OS and PFS curve. This is also consistent with the revised approach presented by the company which uses trifluridine-tipiracil monotherapy as the reference curve to obtain estimates for the combination arm (see Section above). The HRs of trifluridine-tipiracil monotherapy versus regorafenib from the random effects NMA and used in this scenario are 1.01 (95% CI 0.73 – 1.45) for OS and 1.05 (95% CI 0.74 – 1.6) for PFS. The resulting curves are presented in **Figure *4*** and results presented in **Table *1***. In addition, the committee also concluded that it would like to explore treatment waning scenarios, to provide certainty when validating overall survival. This is discussed further in the section below.
3 Treatment waning	In Section 3.9, the committee requested the option to explore treatment waning scenarios in order to provide more certainty when validating overall survival estimates for the trifluridine-tipiracil plus bevacizumab arm when using the preferred approach of HRs applied to trifluridine-tipiracil monotherapy arm. Firstly, it should be noted that there is no evidence from the SUNLIGHT trial which supports the idea of a treatment waning effect, as the KMs show a significant benefit and consistent treatment effect across the observed period. There is also no prior precedent of a treatment waning assumption in any of the prior appraisals in mCRC.[1,6] Despite this, functionality has

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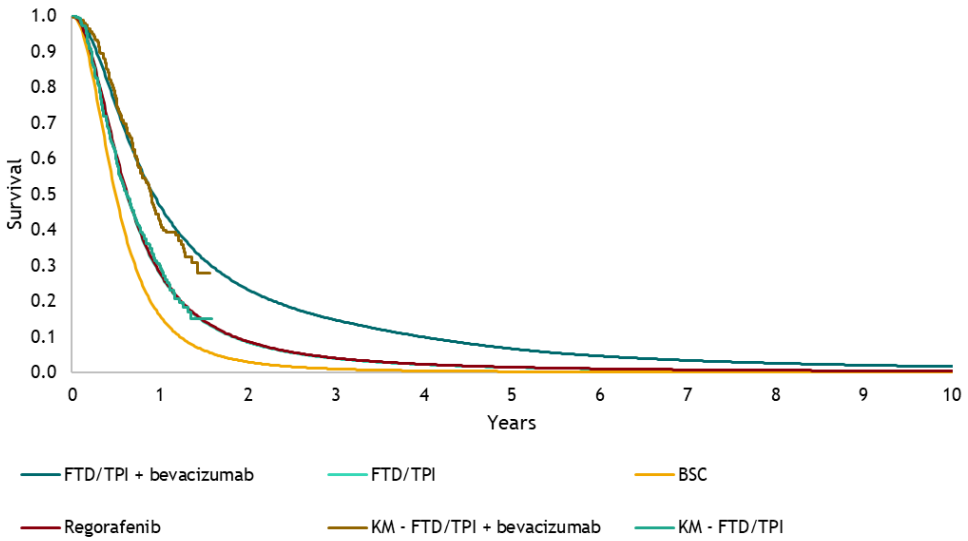
	been included within the updated cost-effectiveness model to consider the impact of treatment waning before the trifluridine-tipiracil plus bevacizumab arm. Within this functionality, the combination arm gradually trends the hazard of death towards the hazard of the trifluridine-tipiracil monotherapy arm over two user amendable time points. As the committee preference is to use trifluridine-tipiracil monotherapy as the reference curve and apply the HR's from the NMA to inform the other treatments, the resulting curves in the revised company base case project outcomes for the trifluridine-tipiracil plus bevacizumab arm which may be slightly optimistic over the entire time horizon duration (e.g., see **Figure *3*** which has a projected survival slightly above the observed data). Taking the committee preferences into account, the treatment waning application has been applied in the revised base case presented by Servier, assuming that treatment waning occurs between years 3-5. 5 years was chosen as the endpoint, acknowledging that a sudden immediate effect would be unlikely. Further to this, the use of a gradual waning effect between 3-5-years was chosen as this has been accepted previously in alternative appraisals[7] (although as mentioned none in mCRC), and further to this, the 5-year point is aligned with the most common timepoint considered in prior appraisals which apply treatment waning assumptions.[8] Servier note however that these timepoints are somewhat arbitrary as there is no evidence to suggest a treatment waning occurs and if it does at which timepoint. The resulting curves applying the treatment waning effect are presented in **Figure *9***. Results including treatment waning are presented in **Table *1***. **Figure 9: Overall survival – HRs applied to trifluridine-tipiracil (SUNLIGHT) – treatment waning applied between 3-5 years.**  Key: BSC, best supportive care; FTD/TPI, trifluridine-tipiracil; HR, hazard ratio; KM, Kaplan-Meier
4 Regorafenib time on treatment	In Section 3.10 of the draft guidance, it states that the committee felt the time on treatment (ToT) for regorafenib would be overestimated if assuming same as treatment until progression, but that the EAG's approach assuming 68% of patients who are progression-free to be on treatment was an underestimate. The committee wanted to see further sensitivity analysis increasing the proportion of patients on treatments. Servier had some concerns over the EAG's approach to model the regorafenib ToT. By assuming a flat proportion are on treatment at any time, the resulting curve looked implausible and assumed a certain percentage didn't receive treatment from cycle 0. This can be seen in

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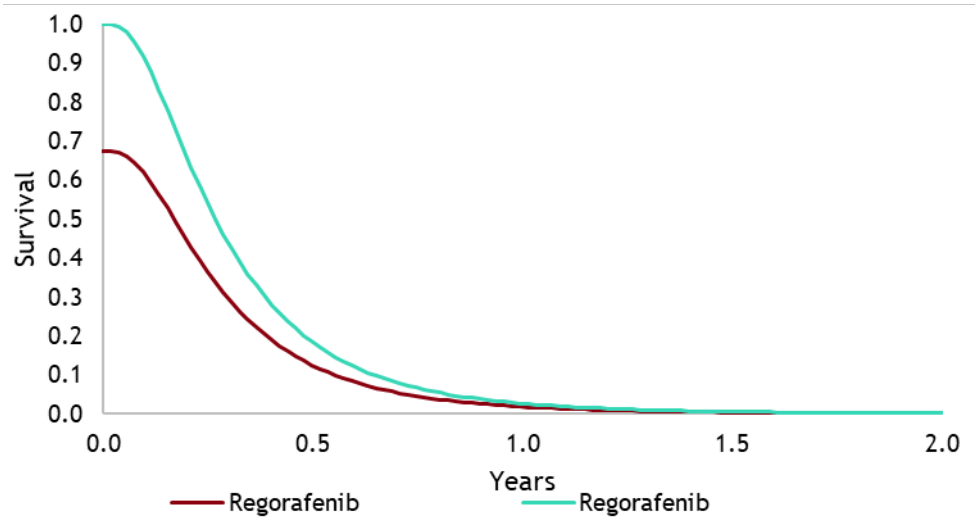
Figure 10 which shows the EAG's ToT curve for regorafenib versus the PFS curve. Servier consider that a more appropriate way to apply an adjustment would be to apply a HR to the regorafenib PFS curve rather than a flat proportion (which avoids assuming >30% of patients never receive a at least 1 dose of regorafenib).

Figure 10: Regorafenib PFS versus ToT (68% of progression-free patients using EAG approach)



Key: PFS, progression-free survival; ToT, time on treatment

Servier agree with the Committee that 68% seems to underestimate the proportion of patients on treatment compared to those who are progression-free for regorafenib. In TA866, in the company's clarification response, they report observed data from the regorafenib trials on PFS and ToT as proportions at 6 months and 1 year. At 6 months, regorafenib's PFS is 15.15% versus 14.85% ToT resulting in a proportion of 98.0%. At 1 year, PFS is 4.67% versus ToT 4.68% resulting in a 100% proportion. In the CORRECT study[9], the median ToT is 1.7 months versus 1.9 months median PFS resulting in a proportion of 89.4%. As such, Servier have developed further scenarios around the proportion of patients on treatment versus those who are progression-free using a different approach to the EAG. These scenarios apply a HR to regorafenib's PFS curve, with the resulting proportion of patients on treatment versus progression-free calculated from the modelled means. The HR used was back calculated based on the aforementioned ToT/PFS proportions from existing data using the revised company base case.

- Scenario 1 uses a HR of 0.97 (resulting in 98.0% being on treatment versus progression-free derived from the CORRECT study difference at 6-months)
- Scenario 2 uses a HR of 0.85 (resulting 89.4% being on-treatment versus progression-free derived from the CORRECT study medians)
- Scenario 3 uses a HR of 0.82 (resulting in 87.5% being on treatment versus progression-free based on median PFS vs ToT from trifluridine-tipiracil monotherapy in SUNLIGHT)

Scenario 2 was used in the Company revised base case as this proportion was based on the data in the CORRECT trial and sits between the two other proportions explored (87.5% and

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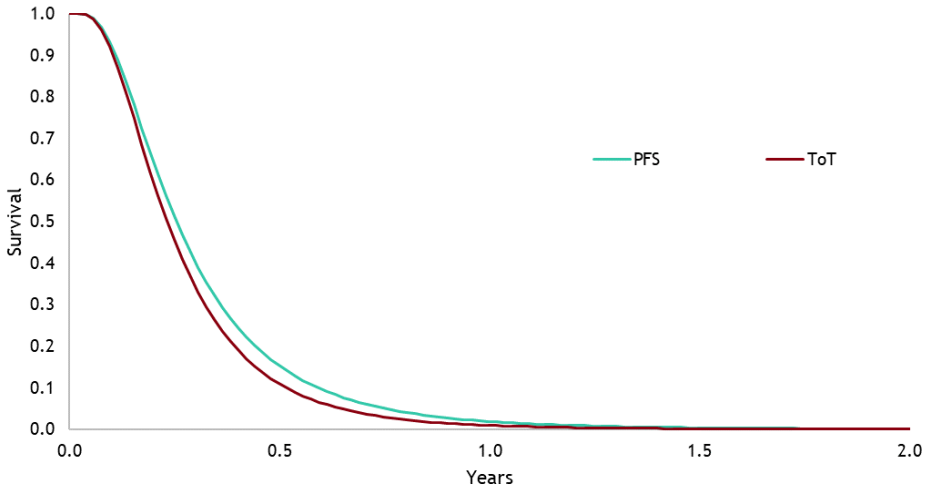
	98%). Figure 11 presents the resulting curves using Scenario 2 for regorafenib with results of all scenarios presented in **Table *1***. **Figure 11: Regorafenib PFS versus ToT using HR approach (HR=0.85; 89.4% ToT vs PFS)**  Key: HR, hazard ratio; PFS, progression-free survival; ToT, time-on-treatment
5 Regorafenib relative dose intensity	In Section 3.11 of the draft guidance, the committee concluded that they preferred using the relative dose intensity (RDI) for regorafenib from the CORRECT study as it was likely to match regorafenib's use in clinical practice. Servier still maintain that the same RDI for trifluridine-tipiracil and regorafenib should be applied particularly in the revised base case using the HRs applied to trifluridine-tipiracil monotherapy, as the outcomes of trifluridine-tipiracil and regorafenib and nearly identical. The resulting ToT curves are also nearly identical. Therefore, given the similarity in outcomes between regorafenib and trifluridine-tipiracil monotherapy, it is expected that the RDI would be similar between the two arms. Servier reiterate that this approach is also consistent with assumptions made in previous mCRC appraisals. In the prior regorafenib appraisal TA866[6], the company was criticised for assuming different RDI for regorafenib and trifluridine-tipiracil. This was due to a large observational study by Nakashima et al, 2020 directly comparing the efficacy and safety of regorafenib and trifluridine-tipiracil, which suggests similar dose reductions for both treatments (54% and 48% respectively).[10] As such the EAG for TA866 preferred to assume equal RDIs for regorafenib and trifluridine-tipiracil and the committee concluded that they preferred the EAGs approach.[6]
6 Bevacizumab cost	The cost-effectiveness of the new technology will improve when lower cost generic / biosimilar formulations of existing therapies become available. Servier understand that the confidential bevacizumab costs were sourced from the commercial medicines unit prior to the meeting on May 15th. However, Servier believe these would have been sourced prior to the EAG report, which was received on 22 February 2024, and therefore under the previous financial year. As the costs are updated on biosimilars and generics on an annual basis, we wanted to check that the most up to date costs of bevacizumab will be sourced and inputted prior to the second committee meeting. In addition, Servier is concerned that a range of costs are being used for bevacizumab and then a range applied. Biosimilars for bevacizumab are available to the NHS at contract prices

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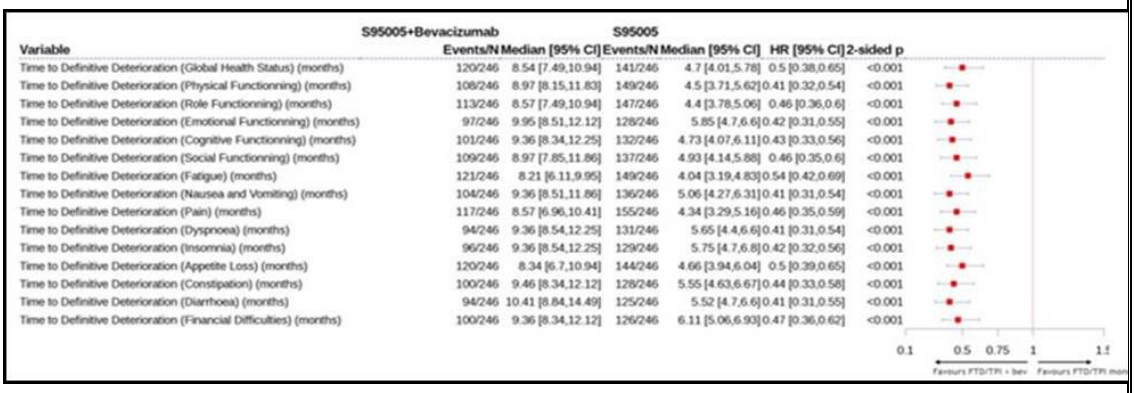
	negotiated through the Commercial Medicines Unit (CMU) – these are lower than the list price but are commercial in confidence. However, different regional CMU prices are available for bevacizumab The company believes the lowest cost should be applied as an efficient use of healthcare resources, and therefore the lowest cost should be applied for the purposes of this appraisal as these costs are only likely to continue to reduce.
7 Utility values	In Section 3.12 of the draft guidance, it states that the committee agreed that the evidence for treatment-specific utility values was not convincing and subsequently preferred pooled utility values for each health state. However, there is strong clinical opinion that based on slower clinical deterioration and the substantial five-fold increase in response rates of trifluridine-tipiracil plus bevacizumab versus trifluridine alone (6.1% vs 1.2%) that quality-of-life is better for patients receiving trifluridine-tipiracil plus bevacizumab. EQ-5D data can be known to have limitations with regard to its sensitivity to health problems, and therefore the measure may not capture the true differences in quality of life.[11,12.] The risk of definitive deterioration based on EORTC QIQ-C30 in SUNLIGHT, shows that across all of the domains (five functional and eight symptom based), the outcomes are significantly better for trifluridine-tipiracil plus bevacizumab (Figure 12). **Figure 12: Risk of definitive deterioration ≥10 points in EORTC QLQ-C30 (SUNLIGHT trial, n=492 [FAS])**  The reduced Risk of Deterioration of quality-of-life favours trifluridine-tipiracil plus bevacizumab vs trifluridine-tipiracil monotherapy based on the “Global Health Status” scale (Figure 13). In addition, the time to deterioration is longer with trifluridine-tipiracil plus bevacizumab compared to trifluridine-tipiracil monotherapy while considering the QLQ-C30 Global Health Status sensitivity analysis (8.5 months versus 4.7 months; HR 0.49, 95% CI: 0.40-0.60). This is much longer than median PFS (5.6 months versus 2.4 months, respectively). This suggests that there is at least around 3 months delay in deterioration after progression. **Figure 13: Risk of Deterioration of quality of life with trifluridine-tipiracil plus bevacizumab**

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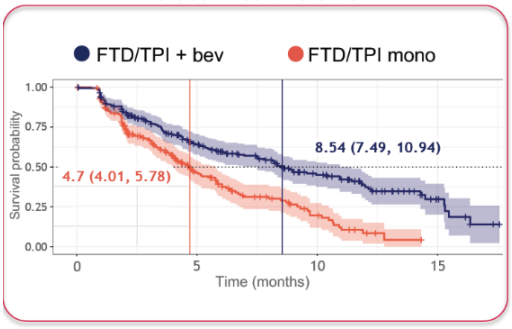
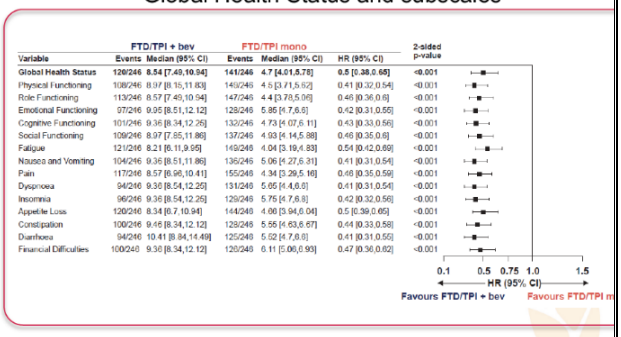
QLQ-C30: time to definitive deterioration by 10 points

Global Health Status



Global Health Status and subscales



Key: FTD/TPI, trifluridine-tipiracil
Source: SUNLIGHT CSR[11]

Thus, Sevier believe there is enough clinical rationale to expect a better quality-of-life for trifluridine-tipiracil plus bevacizumab in the progression-free health state. As part of the interviews, some clinical experts also commented that regorafenib may have worse quality of life in comparison to trifluridine-tipiracil due to increased toxicity and considered that HRQoL would be even lower for BSC patients.
There was uncertainty among the clinicians as to whether a benefit in HRQoL in the PFS state would translate to the progressed state given the lack of evidence in this area. One clinician outlined that a number of things could affect this such as the biology post-progression and next line of treatment. One of the clinicians consulted stated that that there would be a difference in quality of life after progression but that it was likely to be the same after some time. Another clinician believed that quality of life would certainly be different in the progressed state for patients in the regorafenib arm due to ongoing toxicity. Servier agree that post-progression utilities are uncertain and that the difference in patients' quality of life is unknown over time. However, due to the substantial benefit in response rates, it is plausible that patients treated with trifluridine-tipiracil plus bevacizumab have a lower tumour burden upon progression and as such have a better quality of life compared to those patients treated with trifluridine-tipiracil and subsequently regorafenib and BSC.

As there is uncertainty as to treatment effects in the progressed state, a different approach has been incorporated into the cost-effectiveness model. Instead of assuming a utility benefit for trifluridine-tipiracil plus bevacizumab across the entire progressed disease state, the difference lasts for an initial period after progression then the same utility value is assumed for all treatment arms.

To apply this scenario, the model applies a utility increment (to the PD utility value) to the trifluridine-tipiracil plus bevacizumab arm for patients leaving the PFS health state. The utility increment uses the following inputs and assumptions:

- Utility benefit over trifluridine-tipiracil monotherapy
    - This is based on the treatment specific utility value estimated from the SUNLIGHT trial using the EQ-5D regression model coefficient (0.043)
- Time point benefit assumed for

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<table>
<tr><td></td><td>

3 months is explored as this aligns with the difference between median PFS and time to deterioration.

Proportion of patients who progress versus die from the PFS state.

This is calculated using the SUNLIGHT trial where 178 out of the 206 (86.4%) PFS events were progression events over death events in the trifluridine-tipiracil plus bevacizumab arm.

The utility increment is the calculated as:

(Utility benefit x time [months] x % progressed)/12.
This resulted in a utility increment of 0.009 for 3 months.

When this scenario is applied, the progressed utility value for all arms is set to SUNLIGHT – treatment pooled with the utility increment applied to all patients leaving the PFS state for trifluridine-tipiracil plus bevacizumab.
</td></tr>
<tr><td>8 Subsequent treatments</td><td>
In the draft guidance Section 3.13, it states that according to NHS England, the attrition rate between third line and fourth line is around 35% and that the committee concluded that the proportion of patients having subsequent treatment data from NHS England was appropriate for decision making. As such, Servier has revised its base case which assumes 35% of patients receive subsequent treatment on all arms and uses the EAG's preferred distributions, i.e., everyone:

on trifluridine-tipiracil (with or without bevacizumab) had subsequent regorafenib
on the regorafenib arm had subsequent trifluridine-tipiracil alone

The results of the revised base case are presented in **Table *1***.
</td></tr>
<tr><td>9 Severity modifier</td><td>
In Section 3.14 of the draft guidance, it states that the committee considered that the size of the QALY shortfall calculated for trifluridine-tipiracil may have been overestimated if the overall survival extrapolations have been underestimated. In addition, the starting age of 62 (based on SUNLIGHT) may not reflect the average age of people living with mCRC in clinical practice. The committee would like to see more data on the mean age of patients having trifluridine-tipiracil which could be used to inform severity weightings. Based on the scenarios using the observational UK studies to inform the trifluridine-tipiracil survival and HRs from the NMA, the severity modifier has been re-calculated with the corresponding age and sex distribution. The sex distribution was not available for the SACT data so for the calculations it has been assumed the same as SUNLIGHT.

The results are presented below:
<table>
<tr><th rowspan="2">Source</th><th rowspan="2">Patient characteristics</th><th colspan="4">Severity weighting</th></tr>
<tr><th></th><th>Trifluridine-tipiracil</th><th>Regorafenib</th><th>BSC</th></tr>
<tr><td>SUNLIGHT</td><td>Mean age = 62
% female: 48%</td><td>QALYs:
Absolute:
Proportional:
Weighting:</td><td>0.63
11.38
94.75%
x1.2</td><td>0.64
11.37
94.67%
x1.2</td><td>0.45
11.56
96.25%
x1.7</td></tr>
<tr><td>Audit data</td><td>Mean age = [redacted]
% female: [redacted]</td><td>QALYs:
Absolute:
Proportional:</td><td>[redacted]</td><td>[redacted]</td><td>[redacted]</td></tr>
</table>
</td></tr>
</table>

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

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			Weighting:	x1.2	x1.2	x1.7
	Wadd et al, 2022	Mean age= 68 % female: 26%	QALYs: Absolute: Proportional: Weighting:	0.59 9.21 93.98% x1.2	0.60 9.20 93.88% x1.2	0.42 9.38 95.72% x1.7
	Tong et al, 2021	Mean age = 66 % female: 41%	QALYs: Absolute: Proportional: Weighting:	0.55 10.02 94.80% x1.2	0.56 10.01 94.70% x1.2	0.37 10.20 96.50% x1.7
	SACT data	Mean age = 65 % female: 48%*	QALYs: Absolute: Proportional: Weighting:	0.61 10.34 94.43% X1.2	0.61 10.34 94.43% X1.2	0.43 10.52 96.07% X1.2

Key: BSC, best supportive care; QALYs, quality-adjusted life-years
Note: *Assumed same as SUNLIGHT

All the results show applicability for a severity weighting (x1.2 for trifluridine-tipiracil and regorafenib and x1.7 for BSC). As presented in the original submission, when using the data from TA405 (average age 63, 39% female and 11.63 QALYs), trifluridine-monotherapy met the x1.7 severity weighting.

10 Potential misinterpretation	Servier is concerned about the potential misinterpretation of the text in the draft guidance which states ***"The results of an indirect comparison also suggest similar benefits for trifluridine–tipiracil plus bevacizumab compared with regorafenib".*** This sentence may be interpreted to mean that trifluridine-tipiracil plus bevacizumab has similar efficacy to regorafenib. Servier note that the updated NMA provided at clarification stage showed the HR of trifluridine-tipiracil plus bevacizumab versus regorafenib was 0.60 (0.38, 0.95), which demonstrates a clinically significant OS benefit of trifluridine-tipiracil plus bevacizumab versus regorafenib. We would like to request this statement to be rephrased to avoid misinterpretation of evidence.

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.

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- 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.

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Appendix 1: Scenarios and revised company base case

The individual scenarios applied to the previous company base case, and resulting revised company base case are presented in **Table *1***.

Table 1: Scenarios and revised base case results – pairwise analysis (with PAS) – all severity modifiers (no weight, x1.2 and x1.7)

Technologies	Total			Incremental					ICER (£/QALY)		
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs					
						No weight	x1.2	x1.7	No weight	x1.2	x1.7
Scenario 1: Apply HRs from NMA to trifluridine-tipiracil as reference curve (SUNLIGHT)											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.88	1.23								
Trifluridine-tipiracil	[redacted]	0.95	0.62	[redacted]	0.94	0.61	0.73	1.04	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.63	[redacted]	0.93	0.60	0.72	1.02	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.44	[redacted]	1.23	0.79	0.95	1.34	[redacted]	[redacted]	[redacted]
Scenario 2: Apply HRs from NMA to trifluridine-tipiracil as reference curve (Audit)											
Trifluridine-tipiracil + bevacizumab	[redacted]	[redacted]	[redacted]								
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 3: Apply HRs from NMA to trifluridine-tipiracil as reference curve (Wadd et al, 2022)											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.77	1.16								
Trifluridine-tipiracil	[redacted]	0.89	0.58	[redacted]	0.88	0.58	0.69	0.98	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.90	0.59	[redacted]	0.87	0.57	0.68	0.97	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.62	0.41	[redacted]	1.15	0.75	0.90	1.27	[redacted]	[redacted]	[redacted]
Scenario 4: Apply HRs from NMA to trifluridine-tipiracil as reference curve (Tong et al, 2022)											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.77	1.15								

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Technologies	Total			Incremental					ICER (£/QALY)		
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs					
						No weight	x1.2	x1.7	No weight	x1.2	x1.7
Trifluridine-tipiracil	[redacted]	0.82	0.54	[redacted]	0.95	0.61	0.73	1.03	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.84	0.55	[redacted]	0.93	0.60	0.72	1.02	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.54	0.37	[redacted]	1.23	0.78	0.94	1.33	[redacted]	[redacted]	[redacted]
Scenario 5: Apply HRs from NMA to trifluridine-tipiracil as reference curve (SACT data)											
Trifluridine-tipiracil + bevacizumab	[redacted]	[redacted]	[redacted]								
Trifluridine-tipiracil	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BSC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Scenario 6: Treatment waning applied between 3-5 years											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.35	0.94								
Trifluridine-tipiracil	[redacted]	0.95	0.62	[redacted]	0.40	0.32	0.39	0.55	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.56	[redacted]	0.52	0.38	0.46	0.65	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.63	0.42	[redacted]	0.72	0.52	0.62	0.88	[redacted]	[redacted]	[redacted]
Scenario 7: Regorafenib ToT using HR applied to PFS curve (HR = 0.85)											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.35	0.94								
Trifluridine-tipiracil	[redacted]	0.95	0.62	[redacted]	0.41	0.32	0.39	0.55	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.56	[redacted]	0.52	0.38	0.46	0.65	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.63	0.42	[redacted]	0.73	0.52	0.62	0.88	[redacted]	[redacted]	[redacted]
Scenario 8: Treatment independent PFS utility and PD utility benefit for 3 months post progression											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.35	0.94								
Trifluridine-tipiracil	[redacted]	0.95	0.63	[redacted]	0.41	0.31	0.37	0.52	[redacted]	[redacted]	[redacted]

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Technologies	Total			Incremental					ICER (£/QALY)		
	Costs (£)	LYG	QALYs	Costs (£)	LYG	QALYs					
						No weight	x1.2	x1.7	No weight	x1.2	x1.7
Regorafenib	[redacted]	0.83	0.57	[redacted]	0.52	0.37	0.44	0.63	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.63	0.43	[redacted]	0.73	0.51	0.61	0.86	[redacted]	[redacted]	[redacted]
Scenario 9: Subsequent treatment assuming 35% receive treatment; EAG UK-based distribution											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.35	0.94								
Trifluridine-tipiracil	[redacted]	0.95	0.62	[redacted]	0.41	0.32	0.39	0.55	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.56	[redacted]	0.52	0.38	0.46	0.65	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.63	0.42	[redacted]	0.73	0.52	0.62	0.88	[redacted]	[redacted]	[redacted]
Revised company base case (1+6+7+8+9) *											
Trifluridine-tipiracil + bevacizumab	[redacted]	1.69	1.12								
Trifluridine-tipiracil	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, Patient Access Scheme; QALYs, quality-adjusted life years

Notes: *Includes additional monitoring costs for regorafenib and BSC as per the EAG's base case

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Appendix 2: Parametric models fit to UK real-world data.

Audit data

Table 2: Statistical goodness-of-fit scores – Audit data

Parameterisation	Overall survival	
	AIC	BIC
Exponential	2068.9	2072.6
Generalised gamma	2017.2	2028.5
Gompertz	2070.7	2078.2
Log-logistic	2019.7	2027.3
Log-normal	**2015.5**	**2023.0**
Weibull	2054.7	2062.2

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 14: Parametric curve fits – Audit data - OS

Key: KM, Kaplan-Meier; OS, overall survival

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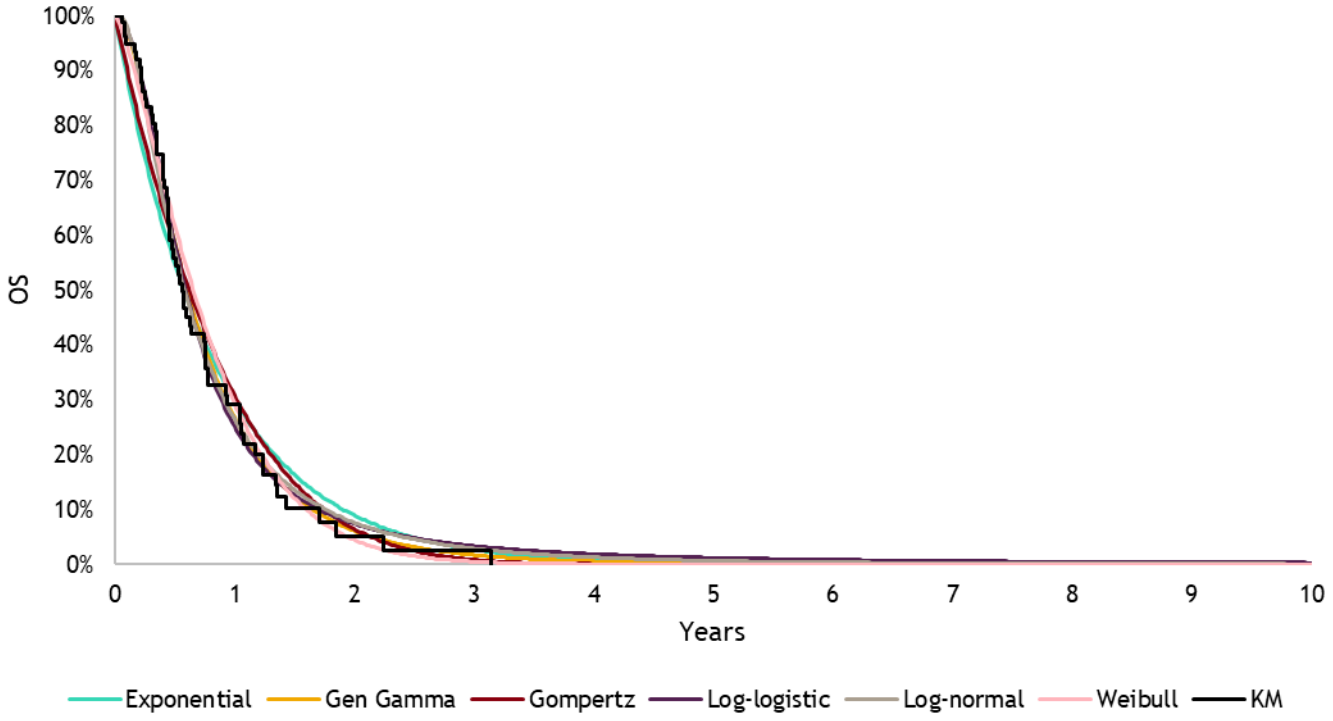
Wadd et al, 2022

Table 3: Statistical goodness-of-fit scores – Wadd et al, 2022

Parameterisation	Overall survival	
	AIC	BIC
Exponential	397.4	399.8
Generalised gamma	388.7	395.7
Gompertz	397.8	402.5
Log-logistic	**386.2**	**390.9**
Log-normal	387.6	392.3
Weibull	391.4	396.0

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 15: Parametric curve fits – Wadd et al, 2022 - OS



Key: KM, Kaplan-Meier; OS, overall survival

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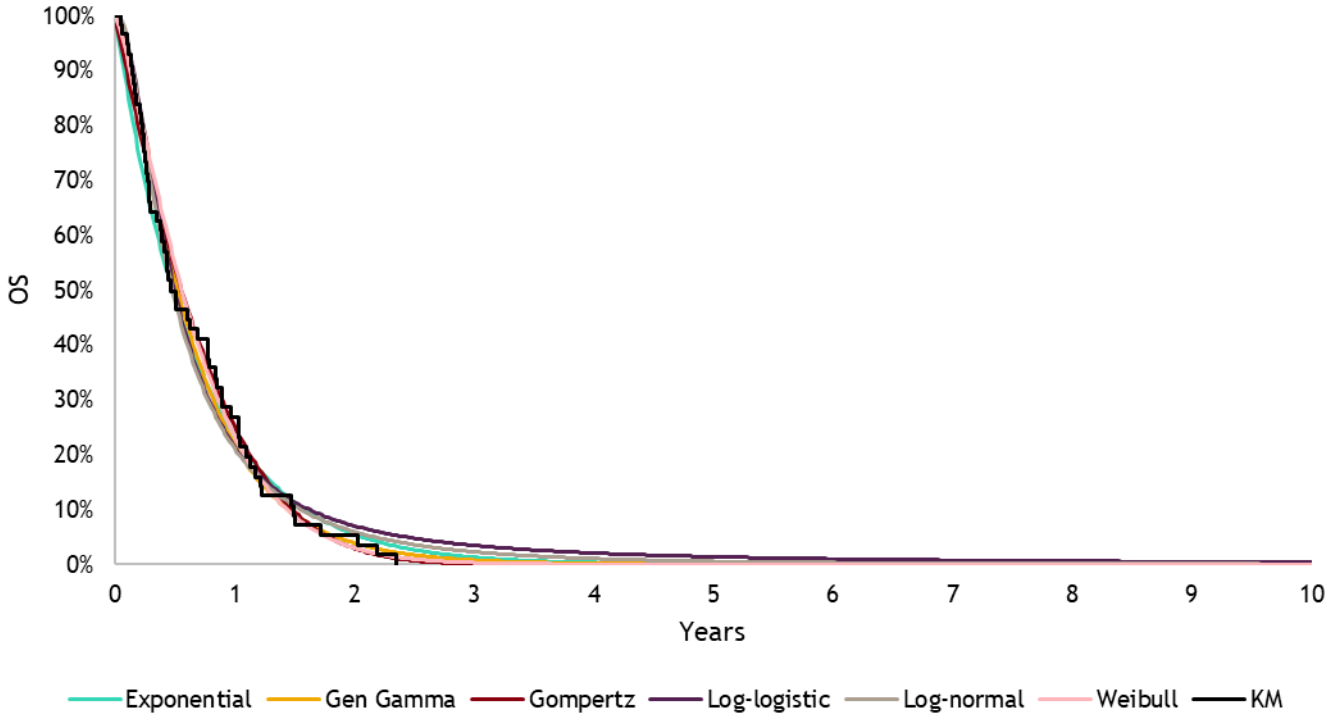
Tong et al, 2021

Table 4: Statistical goodness-of-fit scores – Tong et al, 2021

Parameterisation	Overall survival	
	AIC	BIC
Exponential	350.5	352.5
Generalised gamma	349.0	355.0
Gompertz	349.4	353.5
Log-logistic	351.8	355.8
Log-normal	349.0	353.0
Weibull	**347.8**	**351.9**

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 16: Parametric curve fits – Tong et al, 2021 - OS



Key: KM, Kaplan-Meier; OS, overall survival

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on **27 June 2024**. Please submit via NICE Docs.

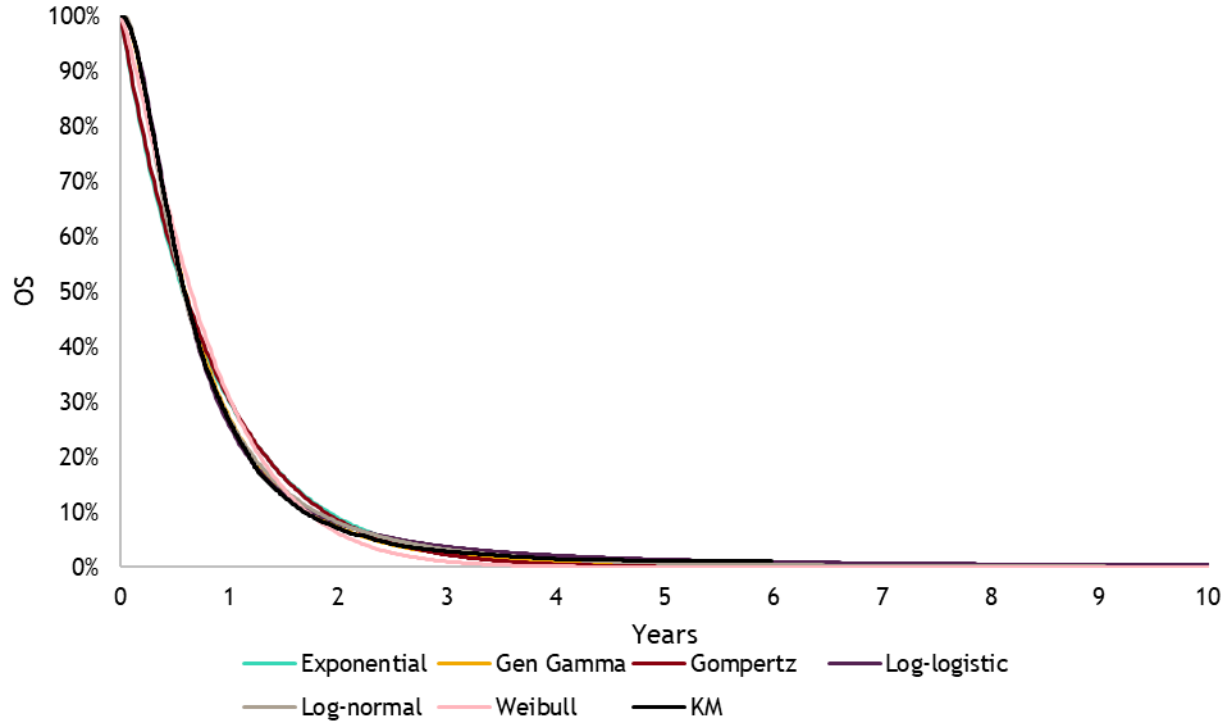
SACT data

Table 5: Statistical goodness-of-fit scores – SACT data

Parameterisation	Overall survival	
	AIC	BIC
Exponential	37065.8	37072.6
Generalised gamma	36099.2	36119.4
Gompertz	37058.3	37071.8
Log-logistic	**36067.6**	**36081.0**
Log-normal	36143.2	36156.7
Weibull	36674.3	36687.7

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion

Figure 17: Parametric curve fits – SACT data - OS



Key: KM, Kaplan-Meier; OS, overall survival

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on **27 June 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):	**Prof Mark Saunders, Consultant GI oncologist, The Christie and Expert on recent NICE Lonsurf / BVZ committee**

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

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.	**I have previously completed the NICE disclosures forms and my disclosures have not changed since then**
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Nil**
Name of commentator person completing form:	**Prof Mark Saunders**

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Draft guidance comments form

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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.
1	**Modelling** It is hard for me as a clinician to argue which is the best model to use. But I would suggest that there is no perfect model and you will have seen many different data-sets which can fit different models. We are also talking about very small differences in graphs that can make significant changes to the outcome / cost-effectiveness. Why should NICEs model be right and the companies wrong? There must be a way to compromise and come up with a model that fits a number of different trial and personal datasets that gives more flexibility and closes the gap between the models from the company and NICE.
2	"**The results of an indirect comparison also suggest similar benefits for trifluridine–tipiracil plus bevacizumab compared with regorafenib"** This is, and I hate to use this, **RUBBISH**. How can anyone come up with this outcome? So, the survival gain for lonsurf and regorafenib in different trials is similar and just over 2 months in the RECOURSE and CORRECT trials. The SUNLIGHT trial shows that Lonsurf / BVZ is significantly better than Lonsurf alone. So how can anyone say from some sort of indirect comparison that Lonsurf / BVZ is equivalent to regorafenib?! This is honestly laughable and makes the NICE process a joke. It is statistics for statistics sake, and they have come up with an obviously wrong outcome. This very result makes me concerned that some of the people involved in producing this guidance have very little knowledge of the management of CRC. NICE want RCTs and "good evidence". So how can one of the factors turning down an effective combination be this "indirect comparison"! Please don't use this as evidence to turn down a good treatment. The whole clinical world (Not just England / Wales) prefers Lonsurf to regorafenib. Are we all wrong and have missed something? We prefer <u>not</u> to use regorafeninb due to its toxicities and lack of effectiveness. It is NOT as good as Lonsurf / BVZ. Your draft guidance will not change this view and is misleading. **UPDATE from ESMO GI 27/6/24** The PRODIGE68 trial (SOREGATT) has just been presented at ESMO GI. This RCT of 234 patients compared lonsurf and regorafenib and there sequencing when switching from one to the other. The survival endpoints (OS/PFS) and safety were similar with both sequencing, but the time to treatment failure (TTF) was if anything better starting with Lonsurf. This again emphasises that regorafenib is no better than lonsurf and can certainly not be the equivalent of lonsurf / BVZ.
3	**Cost of BVZ and extra treatment with Lonsurf / BZ** It is hard for me to comment on the cost of BVZ since this is often variable and some aspects are confidential. Over the last 20 years, colorectal cancer treatments have become simpler using a lot of tablets. Therefore, when we now compare a simple regimen, lonsurf / BVZ, it becomes more complex and costly than our presently used oral treatments.

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	Lonsurf / BVZ is a very simple MONTHLY regimen. They will have bloods each month and attend clinic once per month. The "extra" BVZ will be given 2 weeks later outside the clinics and without any blood tests. I hope this has been taken into account when formulating the cost of this treatment. It is an effective, simple and well tolerated regimen.
4	**A clinician perspective** From attending national and international meetings, it is obvious that Lonsurf / BVZ is widely used in most western world countries. If NICE turn this regimen down, then we will be an outcast and dare I say it, a laughing-stock of the CRC world. I think NICE will lose credibility by accepting both lonsurf and regorafenib with small survival gains (6-7 months compared to BSC 5 months) and then rejecting lonsurf / BVZ which has approximately double these gains (nearly 11 months).
5	**A patient's perspective** Many patients I treat know of this combination and are really looking forward to being able to receive it later this year. There will be a lot of patients who know the basic survival benefits of this therapy and the fact they can have another 3-4 months of good quality life by receiving this well tolerated and effective treatment. They will feel dejected and traumatised by the negative guidance based on uncertain models and indirect comparisons to a treatment very few have faith in.
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.
- 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.

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Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

Draft guidance comments form

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- 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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Single Technology Appraisal

Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [iD6298]

Comments on the draft guidance from patient expert Steve Bennett, nominated by GUTS UK

COMMENTS

NICE is examining the cost effectiveness to the NHS of using trifluridine-tipiracil with bevacizumab to treat mCRC after two previous lines of treatment that have ended because of disease progression or adverse effects.

The proposed treatment was compared with:

- trifluridine-tipiracil alone
- regorafenib
- Best Supportive Care

My reading of the draft paper is that, although there is evidence of the proposed treatment prolonging life in mCRC patients, there are significant:

1) uncertainties in the overall survival modelling
2) separate uncertainties in the calculation of the QALY weightings, given real world clinical experience with respect to
    a. effectiveness of trifluridine-tipiracil alone, and
    b. the mean age of people starting treatment with trifluridine-tipiracil alone,

As a consequence, the evidence currently available to the committee is insufficient to justify recommendation. However, the implication of the request for further analyses is that it is realistic that refined analysis could reverse that judgement. (Is that correct?)

Unless I missed it, there didn't seem to be quantified data available on the patient tolerance of the three drug treatments (there are narrative comments). Are different degrees of toxicity tolerance built into the data in the SELECT study? I assume that by third line treatment, patients may be already coping with debilitating adverse reactions. I'm not clear whether differential tolerance is (or should be) accounted for explicitly.

Although no equalities concerns were raised, I wondered how ethnic genetic response differences (for example) are handled. Were all ethnicities well represented in the trial that forms the starting point for the company's case? Or is it that there is no data, so it is impossible to say?
Uncertainties around the age distribution of patients in scope could underestimate increased benefit to younger patients? This could be addressed within the requested further analysis.

On the specific questions, I would say (notwithstanding my comments above, and within the limits of my understanding):

1) Has all of the relevant evidence been taken into account? Yes
2) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? Yes
3) Are the recommendations sound and a suitable basis for guidance to the NHS? Yes
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?

    1. See comments above. I'm not sure in this context what the threshold for 'unlawful discrimination' would be, given the challenges of establishing a large enough trial cohort.

Single Technology Appraisal

Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [iD6298]

Comments on the draft guidance received through the NICE website

Role	patient
Conflict	none
Comments on the DG:	
I am a stage 4 bowel cancer patient and I have had 2 systemic treatments both with debilitating side effects. The side effects have massively restricted my ability to enjoy a reasonable quality of life. This proposed treatment offers me hope of being able to control my disease and to be able to carry on with "normal" day to day activities, such as being able to work, look after my youngest son, participate in keep fit activities ie enjoy my running again, my boxing, kettlecise and weight training etc, all these activities have been severely impacted by the chemotherapy which I have been receiving for the last 17 months. It would be devastating if this treatment was not made available on NHS. Thank you.	

CONFIDENTIAL

Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]

ADDITIONAL ANLAYSIS FOR ACM2

CONFIDENTIAL

Produced by **Aberdeen HTA Group**

Authors: Dwayne Boyers[1]

1 Health Economics Research Unit, University of Aberdeen, UK

Date completed: **11 July 2024**

Version: **2.0**

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University of Aberdeen, UK
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Strictly confidential: Contains [redacted] information

1 Overview

This document provides the following additional information and analyses ahead of the second appraisal committee meeting for the NICE technology appraisal of Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [ID6298]:

- **Overall survival assumptions and modelling:** EAG commentary and views on the use of SACT data for trifluridine-tipiracil + bevacizumab to represent the reference curve for the economic model, the most appropriate parametric OS extrapolations for the reference curve, the application of hazard ratios from SUNLIGHT / NMA to model treatment benefit, and the use of different treatment waning assumptions
- **Other remaining areas of uncertainty and company response post ACD:** EAG critique of the company's response to all other issues raised in the ACD, including the EAGs assessment of the company's revised analyses against the preferred committee assumptions from ACM1.
- **Severity weighting:** An EAG re-calculation of the severity weighting using SACT data for trifluridine-tipiracil, reflecting real world evidence on the QALY shortfall most likely to be seen in UK clinical practice.

All cost-effectiveness results provided in this document apply commercial in confidence CMU and comparator PAS prices for trifluridine-tipiracil, regorafenib, bevacizumab, and other concomitant and post-progression treatments used in the economic model. All confidential prices are updated to the most current prices, received from NICE in June 2024. In this document, where more than one confidential price is available, the midpoint CMU price is applied. These include new, updated prices for bevacizumab.

Overall survival assumptions and modelling

SACT data for OS reference curve – trifluridine-tipiracil:

In response to consultation around the ACD, the company provided several additional real-world analyses, including the use of SACT data provided by NHS England. The EAG were also provided with these data and have cross-validated the company's approach, obtaining almost identical KM curves. The EAG notes that the KM curves from SUNLIGHT and SACT data are broadly similar, providing some reassurance that the control arm of the company's study is broadly aligned with UK clinical practice outcomes in terms of trifluridine-tipiracil monotherapy. KM data from SACT and SUNLIGHT are compared in Figure 1 below.

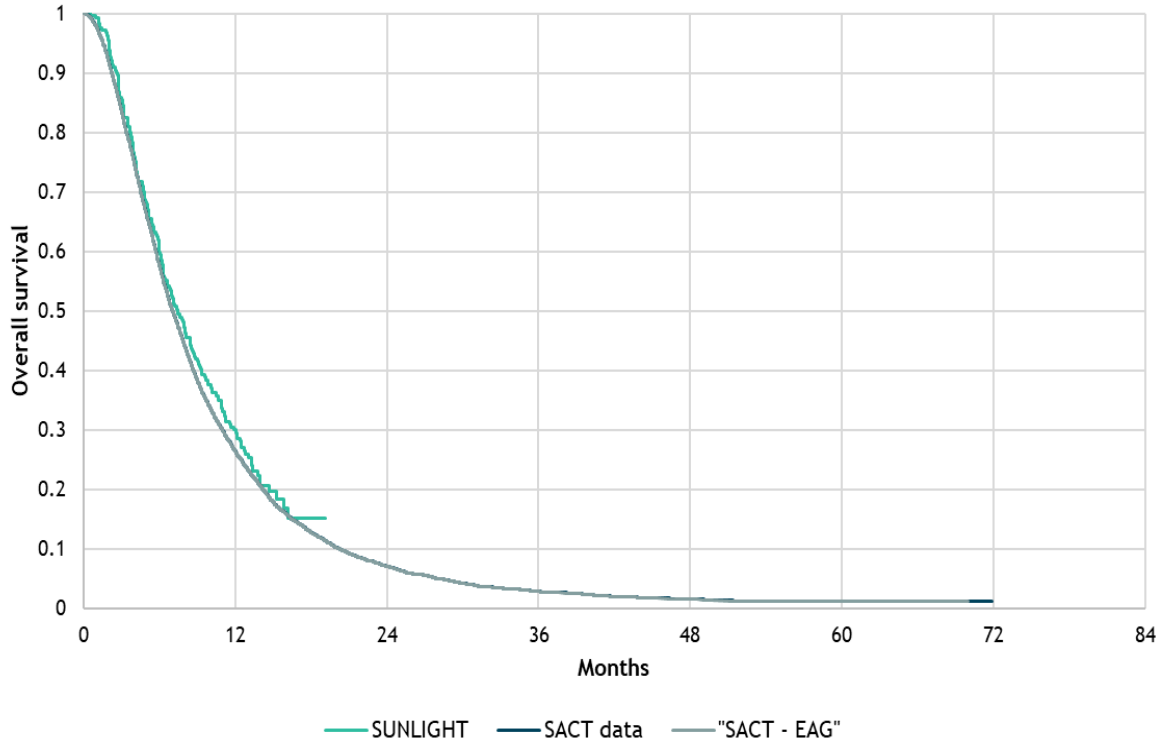

Figure 1 KM curves for sunlight and SACT data

Extrapolation of SACT OS data – trifluridine-tipiracil:

The company fitted six parametric survival curves to the SACT data (Exponential, Gompertz, Weibull, Log Normal, Log Logistic and Generalised Gamma) and assessed the data in terms of visual fit to the KM curves, AIC / BIC statistics of goodness of fit, and comparison of the estimated proportions alive at 1,2,3,5 and 10 years of extrapolation. The EAG's reproduction of the fitted survival curves and assessment of fit can be found in Table 1. Optimal survival

curves in terms of AIC, BIC and closest fit to the KM data are highlighted in grey (bold) for ease of comparison.

Table 1: EAG fitting of curves to SACT data obtained from NICE

	AIC	BIC	Proportion alive at (Years)				
			1	2	3	5	10
KM			26.7%	7.1%	2.8%	1.1%	--
Exponential	16,568	16,575	29.7%	8.8%	**2.6%**	0.2%	0.0%
Generalised Gamma	15,587	15,607	26.9%	**6.9%**	2.2%	0.3%	0.0%
Gompertz	16,553	16,566	30.5%	8.7%	2.3%	0.1%	0.0%
Log-Logistic	**15,568**	**15,581**	25.4%	7.8%	3.6%	**1.3%**	0.3%
Log Normal	15,643	15,656	**26.6%**	7.9%	3.1%	0.7%	0.1%
Weibull	16,140	16,153	30.4%	6.0%	0.9%	0.0%	0.0%

*Note however, that the data are subject to censoring at the end of the KM curve, particularly after 48 months (4 years)

Log logistic provides the best overall fit to the curves, closely followed by generalised gamma. The EAG's view is that both provide reasonable fits to the underlying curves. Generalised gamma provides the best replication of the KM curve at 2 years, with log-logistic being preferred at 5 years. However, it should be noted that there is some censoring of the KM curve data beyond 48 months, meaning that the proportion alive at the very tail of the KM curve at 5 years is likely to be an over-estimation of 5 years OS because not everyone will have reached the full follow-up time period. So whilst, the log-logistic curve provides a closer approximation of the KM proportion, it is unlikely to represent an accurate reflection of true OS at 5 years. The EAG therefore prefers generalised gamma as the appropriate fit to the SACT data because:

1) It is a good statistical fit with acceptable AIC and BIC
2) It provides a closer approximation of the KM OS at key milestones of 2 and 3 years
3) Its projection at 5 years is more plausible because the KM data are an absolute maximum of the proportion that could be alive at 5 years and it is implausible that the log-logistic could lie above the KM curve
4) Longer term projections of a small proportion alive up to 10 years lacks clinical face validity and a curve that tends to 0 should be preferred. The EAG's clinical expert opinion was that, patients receiving current available treatments on the NHS (trifluridine-tipiracil and regorafenib) would not be expected to survive up to 5 years,

and certainly not to 10 years in the extrapolation as suggested with the log-logistic fit to the SACT data.

For the SACT data, the EAG therefore prefers a generalised gamma curve fitted to the data. Direct use of the KM data up to 5 years, followed by the application of the chosen curves is also applied in scenario analysis. Again for this scenario, the generalied gamma is more appropriate as it avoids a small increase in the proportion alive at the tail of the KM curve, a clearly implausible outcome

Whilst numbers are small, the decision to fit a generalised gamma or log logistic OS curve has important implications for the ICER given that a trifluridine-tipiracil + bevacizumab HR is applied to a small proportion alive in the longer term. The use of a log-logistic curve fitted to the SACT data likely extends the OS benefit indefinitely for trifluridine-tipiracil + bevacizumab, and there is insufficient long-term follow up to validate such an extended benefit. The magnitude of bias is unclear but likely favours the intervention by over-estimating QALY gains. On the other hand, when a HR is applied to a reference curve that tends to 0 OS, this places an upper bound on the maximum survival for the trifluridine-tipiracil + bevacizumab OS curve, dropping to 0 at the same point as which the reference curve hits 0. This may provide a bias against the intervention. The EAG view this as one of the limitations of applying HRs over and above independently fitted curves in the economic modelling.

Generalised gamma and log logistic curves fitted to the SACT data for trifluridine-tipiracil monotherapy are compared in Figure 2 below. However, given that differences between the cruves are very difficult to see on the graph, assessment of the table above may be more useful for committee to understand the EAG's long term extrapolation concerns with the log-logistic curve.

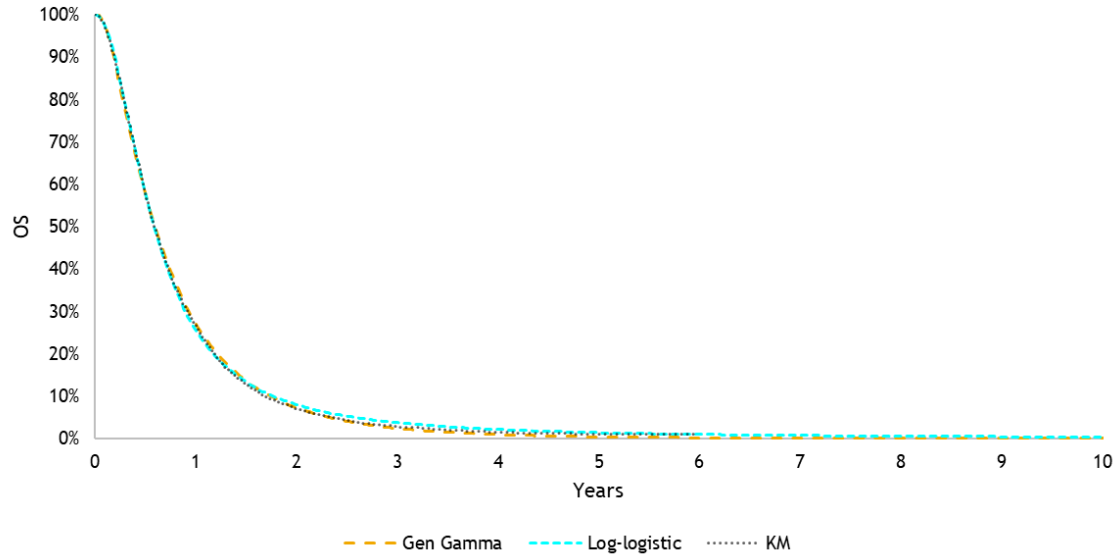

Figure 2: Generalised gamma vs. log-logistic fits to the SACT KM curve data

Summary of company vs. EAG preferred OS assumptions:

Company and EAG preferred analyses for OS are compared in Table 2 below. The ACD provided a clear steer that the committee preferred the use of HRs from that the committee preferred the use

Table 2 Summary of company and EAG preferred OS assumptions

Parameter / Asssumption	Company base case post ACD	EAG revised base case post ACD
Approach to modelling OS benefit	HRs from NMA for all comparisons	HR from SUNLIGHT for trifluridine-tipiracil plus bevacizumab and HR from NMA for remaining comparators (regorafenib and BSC)
Reference curve for OS modelling	Trifluridine-tipiracil arm of the SUNLIGHT study	SACT data for trifluridine-tipiracil
Preferred parametric OS survival curve for tri-tip.	Log-logistic	Generalised gamma
Treatment waning	Yes, from 3-5 years	No treatment waning effect when using generalised gamma for the trifluridine-tipiracil reference curve.

Company and EAG preferred OS endpoints for trifluridine-tipiracil + bevacizumab are compared in Table 3. Figures 3 and 4 provide a comparison of the preferred OS curves.

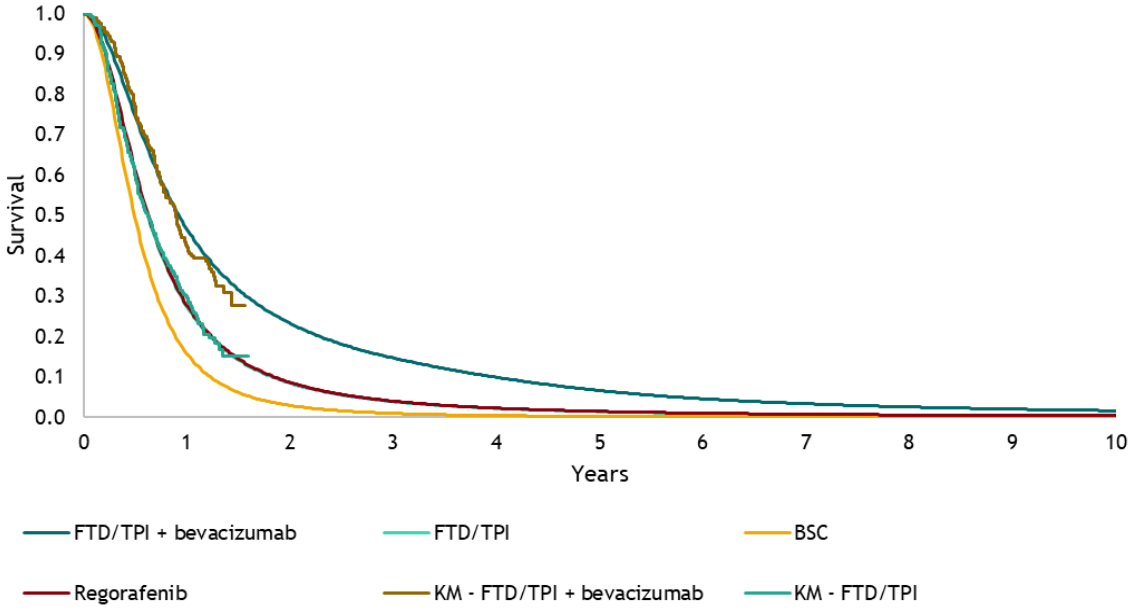

Figure 3 Company preferred OS curves post ACD

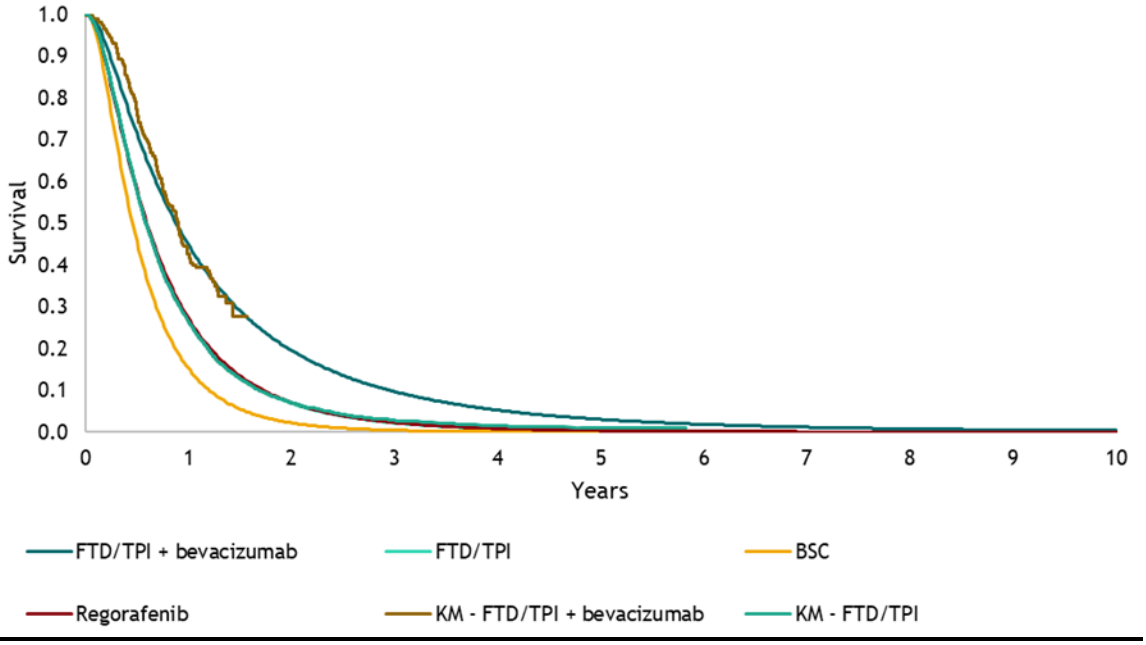

Figure 4 EAG preferred OS curves post ACD

Table 3: OS endpoints in company vs. EAG preferred analyses post ACD

	Proportion alive at (Years)							
	Company				EAG			
	Tri-tip + bev	Tri-tip	Reg	BSC	Tri-tip +bev	Tri-tip	Reg	BSC
1 year	46.9%	27.7%	28.1%	16.0%	44.9%	26.9%	27.3%	15.4%
2 years	23.1%	8.4%	8.6%	2.9%	19.4%	6.8%	7.0%	2.1%
3 years	14.6%	3.8%	4.0%	1.0%	9.6%	2.2%	2.2%	0.4%
4 years	9.9%	2.2%	2.3%	0.4%	5.2%	0.8%	0.8%	0.1%
5 years	6.6%	1.4%	1.5%	0.2%	3.0%	0.3%	0.3%	0.0%
10 years	1.6%	0.3%	0.4%	0.0%	0.3%	<0.1%	<0.1%	<0.1%

The EAG note that the company's base case analysis post ACD applied a HR of death for trifluridine-tipiracil + bevacizumab vs. trifluridine-tipiracil monotherapy that is obtained from the random-effects NMA (0.59). The EAG's interpretation of the ACD is that the committee wanted to also see results of a cost-effectiveness analysis where the the HR from the SUNLIGHT trial (0.61) was used for the comparison between tri-tip + bev vs. tri-tip, but with the HRs from the random-effects NMA applied for the other comparators (regorafenib and BSC). The EAG appreciates that the results are very similar, but an analysis using the trial HR for the trial comparators with the HRs from the NMA for the remaining comparators is provided for completeness.

The magnitude of OS benefit observed for trifluridine-tipiracil plus bevacizumab at 1 year are similar in both the company and EAG preferred base case analyses. However, the magnitude of benefit continues to increase beyond the trial follow up under the company's preferred modelling assumptions, and the EAG view is that this is not sufficiently offset by a treatment waning effect applied between years 3 and 5. The EAG are concerned that there is insufficient evidence available to validate the modelled magnitude of long-term benefit. Therefore, the company's scenarios are likely to present an optimistic scenario with an ICER likely to be at the lower end of a plausible range. The EAG prefers the use of a more conservative set of assumptions, where the trifluridine tipiracil monotherapy reference curve from the SACT dataset is fitted with a generalised gamma parametric survival curve. Given that the generalised gamma provides more pessimistic outcomes in the reference curve, the EAG view is that a treatment waning effect may not be appropriate as it curtails the potential for trifluridine-tipiracil + bevacizumab to generate any additional benefit beyond the point at

which the reference curve tends to 0. The EAG considered applying a treatment waning effect starting at one year because SUNLIGHT KM curves are heavily censored beyond one year, with limited evidence to support sustained benefit over time. This is aligned with the PFS curves which appear to start to converge after 1 year. Logically, one would expect the magnitude of OS benefit to reduce once the cohort progresses and treatment is discontinued. However, the EAG believes that a treatment waning effect would only be necessary if committee prefer the log-logistic curve fitted to the SACT data to offset the indefinite benefit derived when using that curve without treatment waning applied.

Other remaining areas of uncertainty and company response post ACD

Regorafenib time on treatment

The EAG acknowledges the company's concerns regarding the shape of the ToT curve in the EAG's preferred base case analysis. Whilst the EAG's ToT curve for regorafenib drops initially, it fits the ToT curve as a flat proportion of the PFS curve in a way that ensures close alignment with the reported mean (and also the median) time on treatment from the CORRECT study for regorafenib. Under the EAG's initial base case set of modelling assumptions, this proportion was, as the company have correctly identified calculated at 68%. However, this proportion adapts with the other modelling assumptions, and when applying the NMA HRs to estimate PFS, the proportion on treatment for regorafenib is calculated at 72% of the PFS curve using the EAG's approach. If committee consider the time on treatment from the CORRECT study to be a fair reflection of regorafenib treatment discontinuation in UK clinical practice, then the EAG continue to prefer our original approach because it aligns regorafenib treatment acquisition costs with the modelled benefits.

In the company revised base case analysis, the company applies a HR for ToT vs. PFS to the regorafenib PFS curve. The proportion on treatment is first calculated using the ratio of median ToT (1.7 months) to median PFS (1.9 months), 89.4% from the CORRECT study. The ToT HR applied to the regorafenib PFS curve is then back calculated using the company preferred base case assumptions to ensure that the mean modelled time on regorafenib is equal to 89.4% of the mean modelled PFS time. The company's approach leads to an ICER vs. regorafenib which is very similar to simply applying a flat proportion of medians from the CORRECT study.

The EAG understand the logic of the approach put forward by the company. However, the approach taken makes use of medians, not means reported from the CORRECT study. Therefore the company's approach over-estimates the mean time on treatment (15.14 weeks) compared to the mean reported from the CORRECT study (12.175 weeks). The EAG is of the view that treatment acquisition costs should be based on means, rather than medians. Therefore, despite the unsual, shape to the EAG's treatment discontinuation curve, we retain the view that our approach is the most plausible because it best replicates the available median and mean data from the CORRECT study. The issue of the implausible shape to the EAG's curve is not an important driver of cost-effectiveness. That is because the number of years is less than 1 and any errors that might occur due to discounting do not apply.

Regorafenib relative dose intensity

The committee preferred the EAG's approach of applying the relative dose intensity from the CORRECT study. The company response to ACD argues that because the outcomes between tri-tip monotherapy and regorafenib are very similar, then the RDIs should also be similar. The EAG does not consider this a strong argument in favour of the company's approach. One expert advisor commenting on the ACD has reiterated concerns that regorafenib is associated with toxicity in this patient population and the EAG's clinical expert also confirms that dose adjustments would be required in UK clinical practice, meaning that it is highly likely that the RDI for regorafenib would be lower than for trifluridine-tipiracil in UK clinical practice. Indeed, the EAG included additional monitoring costs in the regorafenib arm to account for these toxicity concerns. The EAG maintains the view that the RDI from the CORRECT study should be applied for regorafenib.

Bevacizumab treatment acquisition costs

The EAG thank the company for raising the point that confidential CMU prices should be updated to the current financial year. The EAG has provided committee with a confidential appendix applying the updated bevacizumab prices, following NICE guidance on handling variation in price across the country.

Bevacizumab treatment administration costs

One issue that was raised in the EAG report was uncertainty around the most appropriate HRG code for bevacizumab treatment administration in UK clinical practice. This issue was

not explicitly addressed in the ACD, but could be an important consideration for decision making, worthy of further discussion. The company base case analysis uses HRG code SB12Z, deliver simple parenteral chemotherapy at first attendance, with an NHS reference cost (2021/22) of £286.71, and an NHS payment scheme 2023/24 payment of £167.00. The EAG agrees with the company base case analysis to use NHS reference costs rather than NHS payments data. This is consistent with Section 4.4 of the NICE methods guide. However there remains some uncertainty whether the cost of subsequent administration of bevacizumab would be equivalent to that of a first administration in a treatmen cycle. There is one single NHS reference cost (SB15Z) for delivering subsequent elements of a chemotherapy cycle, with a reference cost of £368.44. However, the EAG does not consider this appropriate for modelling because it covers a wide range of chemotherapy delivery from simple to the most complex and the unit cost is substantially higher than an initial administration. It is therefore unlikely to capture the true opportunity cost of resource use required for subsequent administrations within a cycle. The EAG therefore agrees with the company's base case use of NHS reference cost SB12Z for all administrations. An alternative approach for exploration, with lower costs, might be to use HRG code WF01A, which is a non-admitted nurse led face-to-face medical oncology service, with a unit cost of £158.50. The EAG are unclear as to whether this would be appropriate for bevacizumab administration, but may be worthy of discussion because the treatment administration costs used in the model are an important driver of the ICER. A scenario analysis is provided for committee's information.

Health state utility values

The committee preferred the EAG base case HSUV assumptions which applied treatment pooled HSUVs. The company have provided evidence in response to the factual accuracy check of the EAG report and again in response to ACD noting the clinical improvement that patients experience with trifluridine-tipiracil plus bevacizumab. The EAG fully accepts this statement, but notes that the quality of life benefit is already captured in the model through the additional utility gains from extended PFS. The company points to a longer time period until deterioration in the QLQ global health status outcome than for PFS. However, the EAG notes that this is true in both the tri-tip + bev and tri-tip arms of the study and that the difference between arms is actually quite similar for the QLQ-C30 and for PFS. The company's provided regression analyses in response to clarification provide no strong

evidence in support of treatment specific health state utility values in either the PFS or PPS states. The EAG therefore retains its original position that treatment pooled HSUVs are the most appropriate approach for modelling quality of life benefit.

The EAG notes that the company and EAG preferred HSUVs both use the data from the SUNLIGHT trial. Alternative HSUVs are also available from previous TAs and it may be useful to consider the uncertainty surrounding utilities, particularly for the severity calculation. The full range of HSUVs available for consideration are summarised in Table 4 below.

Table 4: Alternative HSUV data sources

Health state	SUNLIGHT treatment pooled	SUNLIGHT treatment independent (tri-tip + bev)	SUNLIGHT treatment independent (tri-tip)	TA866	TA405
PFS	0.76	0.779	0.737	0.72	0.73
PPS	0.68	0.702	0.659	0.59	0.64

Severity weighting

Table 5 compares the trifluridine-tipiracil + bevacizumab severity weighting using alternative assumptions applied in the company and EAG preferred base cases. The severity weighting applied is a function of age, gender and remaining QALYs in the current standard of care. The EAG provides calculations using different OS extrapolation assumptions, SACT vs. SUNLIGHT data and considers lower utilities from previous TAs for regorafenib and trifluridine-tipiracil for completeness. EAG calculations of QALY weightings are calculated using the York QALY shortfall calculator.

Table 5: Severity weighting for trifluridine-tipiracil monotherapy (Company vs. EAG base case post ACM1)

	SUNLIGHT data (Log-logistic OS, treatment specific HSUVs) – Co. base case	SUNLIGHT data (Generalised gamma OS, treatment specific HSUVs)	SACT data (Log-logistic OS, treatment pooled HSUVs)	SACT data (Generalised gamma OS, treatment pooled HSUVs) – EAG base case	EAG base case + TA866 HSUVs	EAG base case + TA405 HSUVs
Age	61.68	61.68	65**	65**	65**	65**
Proportion female	48.0%	48.0%	48%*	48%*	48%*	48%*
Remaining discounted QALYs	0.63	0.60	0.61	0.57	0.51	0.54
Absolute shortfall	11.38	11.41	10.34	10.38	10.95	10.41
Proportional shortfall	94.75%	95.00%	94.43%	94.79%	95.34%	95.07%
Severity weighting	X1.2	X1.7	X1.2	X1.2	X1.7	X1.7

* Assumption – The EAG does not have access to the gender breakdown. However, this is unlikely to change any conclusions; proportional shortfall ranges from 94.72% (all male) to (94.87% all female) under the EAG preferred assumptions applied to the SACT data.

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

Table 6 Deterministic ICERs, pairwise comparisons, confidential prices applied.

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
0. Company revised base case (HRs from NMA applied to SUNLIGHT; Treatment waning 3-5 years; Regorafenib ToT as HR (0.85) to PFS curve; treatment independent PFS utility; PD tx. Utility benefit for 3 months; NHSE 35% post progression treatment.											
FTD/TPI + bevacizumab	[redacted]	1.69	1.12								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
1. Treatment specific RDIs											
FTD/TPI + bevacizumab	[redacted]	1.69	1.12								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
2. Regorafenib ToT – exponential to median											
FTD/TPI + bevacizumab	[redacted]	1.69	1.12								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
3. Regorafenib ToT - EAG approach (apply a proportion to the PFS curve that replicates the mean ToT from the CORRECT study), 71.9% in the EAG base case.											
FTD/TPI + bevacizumab	[redacted]	1.69	1.12								

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
4. Scenarios 1+3 combined											
FTD/TPI + bevacizumab	[redacted]	1.69	1.12								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.74	0.49	0.59	0.84	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.68	0.81	1.15	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.73	0.48	0.58	0.82	[redacted]	[redacted]	[redacted]
5. Generalised gamma OS curve for trifluridine-tipiracil as reference curve (SUNLIGHT data)											
FTD/TPI + bevacizumab	[redacted]	1.48	1.02								
FTD/TPI	[redacted]	0.89	0.60	[redacted]	0.59	0.41	0.50	0.70	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.65	0.44	[redacted]	0.83	0.57	0.69	0.98	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.90	0.61	[redacted]	0.58	0.41	0.49	0.69	[redacted]	[redacted]	[redacted]
6. SACT data for trifluridine-tipiracil OS											
FTD/TPI + bevacizumab	[redacted]	1.64	1.09								
FTD/TPI	[redacted]	0.90	0.60	[redacted]	0.74	0.49	0.59	0.83	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.62	0.42	[redacted]	1.02	0.67	0.80	1.13	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.91	0.61	[redacted]	0.73	0.48	0.58	0.81	[redacted]	[redacted]	[redacted]
7. Scenarios 5 + 6 combined											
FTD/TPI + bevacizumab	[redacted]	1.35	0.94								

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
FTD/TPI	[redacted]	0.83	0.56	[redacted]	0.52	0.38	0.45	0.64	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.74	0.52	0.63	0.89	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.57	[redacted]	0.51	0.37	0.44	0.63	[redacted]	[redacted]	[redacted]
8. Remove OS treatment waning effect											
FTD/TPI + bevacizumab	[redacted]	1.88	1.21								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.94	0.58	0.70	0.99	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.23	0.77	0.92	1.30	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.93	0.57	0.69	0.98	[redacted]	[redacted]	[redacted]
9. OS Treatment waning effect from 1-2 years											
FTD/TPI + bevacizumab	[redacted]	1.39	0.96								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.45	0.33	0.39	0.56	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	0.74	0.51	0.61	0.87	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.44	0.32	0.38	0.54	[redacted]	[redacted]	[redacted]
10. Apply the HR from the SUNLIGHT trial for the OS and PFS comparisons of trifluridine-tipiracil + bevacizumab vs. trifluridine-tipiracil monotherapy											
FTD/TPI + bevacizumab	[redacted]	1.63	1.09								
FTD/TPI	[redacted]	0.95	0.63	[redacted]	0.69	0.46	0.55	0.78	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	0.98	0.64	0.77	1.10	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.64	[redacted]	0.67	0.45	0.54	0.77	[redacted]	[redacted]	[redacted]

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
11. Treatment pooled HSUVs, including removal of PD utility benefit at transition to progressed.											
FTD/TPI + bevacizumab	[redacted]	1.69	1.10								
FTD/TPI	[redacted]	0.95	0.64	[redacted]	0.74	0.47	0.56	0.79	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.66	0.45	[redacted]	1.03	0.65	0.78	1.11	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.96	0.65	[redacted]	0.73	0.46	0.55	0.78	[redacted]	[redacted]	[redacted]
12. EAG tentative base case (Scenarios 4 + 7 + 8 + 10 + 11 combined), Regorafenib RDI from CORRECT study, mean CORRECT study ToT, Pooled HSUVs, generalised gamma curve fitted to SACT OS data for trifluridine-tipiracil monotherapy, no treatment waning effect, HRs from SUNLIGHT for tri-tip + bev, HRs from NMA for remaining comparators)											
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
SCENARIOS APPLIED TO EAG BASE CASE POST ACD											
13. KM curves from SACT data up to 4 years, with generalised gamma thereafter.											
FTD/TPI + bevacizumab	[redacted]	1.44	0.97								
FTD/TPI	[redacted]	0.85	0.58	[redacted]	0.59	0.39	0.46	0.66	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.83	0.55	0.65	0.93	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.86	0.59	[redacted]	0.58	0.38	0.45	0.64	[redacted]	[redacted]	[redacted]
14. TA405 HSUVs											
FTD/TPI + bevacizumab	[redacted]	1.35	0.87								

	Total			Incremental					ICER	ICER	ICER
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)	(£/QALY) (x1.0)	(£/QALY) (x1.2)	(£/QALY) (x1.7)
FTD/TPI	[redacted]	0.83	0.54	[redacted]	0.53	0.33	0.40	0.57	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.40	[redacted]	0.75	0.47	0.57	0.81	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.55	[redacted]	0.52	0.33	0.39	0.55	[redacted]	[redacted]	[redacted]
15. TA866 HSUVs											
FTD/TPI + bevacizumab	[redacted]	1.35	0.83								
FTD/TPI	[redacted]	0.83	0.51	[redacted]	0.53	0.32	0.39	0.55	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.38	[redacted]	0.75	0.46	0.55	0.78	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.52	[redacted]	0.52	0.31	0.38	0.53	[redacted]	[redacted]	[redacted]
16. Apply OS treatment waning effect from 1-2 years											
FTD/TPI + bevacizumab	[redacted]	1.15	0.80								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.33	0.23	0.28	0.40	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.55	0.38	0.46	0.65	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.32	0.23	0.27	0.39	[redacted]	[redacted]	[redacted]
17. Apply OS treatment waning effect from 3-5 years											
FTD/TPI + bevacizumab	[redacted]	1.31	0.89								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.48	0.32	0.39	0.55	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.70	0.47	0.57	0.80	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.47	0.32	0.38	0.54	[redacted]	[redacted]	[redacted]
18. Bevacizumab treatment administration costs (HRG WF01A, nurse led clinic)											

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
19. Bevacizumab treatment administration costs (SB12Z for initial; SB15Z for subsequent)											
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
20. Bevacizumab treatment administration costs (SB17Z for all)											
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
21. Bevacizumab treatment administration costs (Average of 19 and 20)											
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
22. Bevacizumab NHS payment scheme prices											

	Total			Incremental					ICER (£/QALY) (x1.0)	ICER (£/QALY) (x1.2)	ICER (£/QALY) (x1.7)
	Costs (£)	LYs	QALYs	Costs (£)	LYs	QALYs (x1)	QALYs (x1.2)	QALYs (x1.7)			
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]
23. 21 + 22 combined (NHS payment scheme prices, with average of different HRGs suggested by NHSE)											
FTD/TPI + bevacizumab	[redacted]	1.35	0.92								
FTD/TPI	[redacted]	0.83	0.57	[redacted]	0.53	0.35	0.42	0.59	[redacted]	[redacted]	[redacted]
BSC	[redacted]	0.61	0.42	[redacted]	0.75	0.50	0.60	0.85	[redacted]	[redacted]	[redacted]
Regorafenib	[redacted]	0.83	0.58	[redacted]	0.52	0.34	0.41	0.58	[redacted]	[redacted]	[redacted]

Key: ACD, appraisal consultation document; FTD/TPI, trifluridine-tipiracil monotherapy; HR, hazard ratio; HSUV, health state utility values; ICER, incremental cost-effectivenes ratio; KM, Kaplan Meier; LYs, life years; NMA, network meta analysis; OS, overall survival; PD, progressed disease; PFS, progression free survival; QALY, quality adjusted life years; RDI, relative dose intentisty; ToT, time on treatment.