

# Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments

Technology appraisal guidance

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# 1 Recommendation

- 1.1 Trifluridine–tipiracil with bevacizumab is recommended, within its marketing authorisation, for treating metastatic colorectal cancer in adults who have had 2 lines of treatment (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, antivascular endothelial growth factor or anti-epidermal growth factor receptor treatments). Trifluridine–tipiracil with bevacizumab is only recommended if the company provides trifluridine–tipiracil according to the [commercial arrangement](#).

## Why the committee made this recommendation

Standard treatment for metastatic colorectal cancer after 2 lines of treatment includes trifluridine–tipiracil alone or regorafenib.

The results of a clinical trial show that, compared with trifluridine–tipiracil alone, trifluridine–tipiracil plus bevacizumab increases how long people have before their cancer gets worse and how long they live. The results of an indirect comparison also suggest that trifluridine–tipiracil plus bevacizumab increases how long people have before their cancer gets worse and how long they live compared with regorafenib.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE normally considers an acceptable use of NHS resources. So, trifluridine–tipiracil plus bevacizumab is recommended.

## 2 Information about trifluridine–tipiracil plus bevacizumab

### Marketing authorisation indication

- 2.1 Trifluridine–tipiracil (Lonsurf, Servier Laboratories) plus bevacizumab is indicated for 'the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents'.

### Dosage in the marketing authorisation

- 2.2 The dosage schedules are available in the [summary of product characteristics for trifluridine–tipiracil](#) and the [summary of product characteristics for bevacizumab](#).

### Price

- 2.3 The list price of trifluridine–tipiracil (15 mg/6.14 mg) is £500.00 per 20-tablet pack and £1,500.00 per 60-tablet pack (excluding VAT; BNF online accessed July 2024). The list price of trifluridine–tipiracil (20 mg/8.19 mg) is £666.67 per 20-tablet pack and £2,000.00 per 60-tablet pack (excluding VAT; BNF online accessed July 2024).
- 2.4 The list price of bevacizumab (25 mg/ml) varies between £205.55 and £242.66 per 4-ml vial, and between £810.10 and £924.40 per 16-ml vial (excluding VAT; BNF online accessed July 2024).
- 2.5 The company has a [commercial arrangement](#). This makes trifluridine–tipiracil available to the NHS with a discount. The size of the discount is commercial in confidence.

- 2.6 There is a discount for bevacizumab agreed with the Medicines Procurement and Supply Chain. The prices agreed through the framework are commercial in confidence.

## 3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Servier, a review of this submission by the external assessment group (EAG), and responses from stakeholders. Also, as part of the further analyses requested by committee at the draft guidance consultation, real-world data on the use of trifluridine–tipiracil alone in the NHS in England from the Systemic Anti-Cancer Therapy (SACT) dataset was presented. This was used to address some of the uncertainties identified by the committee about overall survival (OS) for current standard care with trifluridine–tipiracil. See the [committee papers](#) for full details of the evidence.

### Metastatic colorectal cancer

#### The condition and experiences of people with it

- 3.1 Metastatic colorectal cancer (mCRC) is an adenocarcinoma of the colon or rectum that has spread beyond the large intestine, most often to the liver, lung or peritoneum. The patient experts explained that colorectal cancer is also associated with poor long-term survival rates unless people have a diagnosis and treatment at earlier stages of the condition. They also noted that the ability to diagnose the condition and treat it as early as possible may differ across NHS trusts. This can result in variable access to services that would prevent progression to metastatic disease. Both the patient and clinical experts outlined the significant impact on quality of life and severity of the side effects associated with existing mCRC treatment options. They also noted the difficulty in balancing treatment effectiveness with toxicity. The committee agreed that there is an unmet clinical need for treatments with better outcomes for people with mCRC, who would welcome new treatment options.

## Clinical management

### Treatment options

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

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

The initial treatment choice depends on the presence or absence of 3 molecular markers: BRAF V600E, RAS wild-type, and microsatellite instability or mismatch repair deficiency. When these molecular markers are



present, specific biological treatments and chemotherapy are usually offered as first- and second-line treatments. In the absence of these molecular markers, the committee understood that treatment for mCRC consists of various combinations or sequences of chemotherapy agents including FOLFOX (folinic acid plus fluorouracil plus oxaliplatin), CAPOX (capecitabine plus oxaliplatin) and FOLFIRI (folinic acid plus fluorouracil plus irinotecan). For this evaluation, the company positioned trifluridine–tipiracil plus bevacizumab for use at third line or later, in line with the marketing authorisation (see [section 2.1](#)). The EAG agreed with this positioning. But, it highlighted that defining third-line treatment is difficult and depends on the combination of previous chemotherapy agents used. The clinical experts also highlighted that combinations of chemotherapy may be used in a course of treatment, which increases the difficulty in defining lines of treatment in mCRC. For example, there is increased use of FOLFOXIRI, which uses both oxaliplatin and irinotecan. They thought that a better definition for implementing the marketing authorisation would be after both oxaliplatin and irinotecan had been trialled. The committee concluded that this positioning as a treatment at third line or later was clinically appropriate. But, it noted the potential for concerns about the generalisability of the trial evidence to NHS clinical practice because of differences in treatment combinations given earlier in the pathway.

## Comparators

- 3.3 The company's proposed comparators were fewer than the treatment options listed in the NICE final scope. The company proposed trifluridine–tipiracil alone, regorafenib and best supportive care as comparators. This was because they reflect clinical practice and are in line with [NICE's technology appraisal guidance on regorafenib for previously treated mCRC](#). The Cancer Drugs Fund lead explained that trifluridine–tipiracil alone has a better toxicity profile than regorafenib. They added that, although people may have sequential treatment with regorafenib and trifluridine–tipiracil alone in either order, most will have trifluridine–tipiracil alone first. The patient experts highlighted that choice of treatments for people with mCRC is an important consideration. They added that the choice of regorafenib or trifluridine–tipiracil alone may be affected by how physically well the person is and the toxicity profile of the treatment. The clinical

experts explained that, for some people with mCRC, regorafenib would be a more suitable choice of treatment at third line than trifluridine–tipiracil alone. But, the clinical experts also explained that people eligible for best supportive care would generally not be well enough to have active treatment (including trifluridine–tipiracil plus bevacizumab). The committee concluded that, in clinical practice, the choice between trifluridine–tipiracil alone and regorafenib depends on the person with mCRC's choice and clinical judgement, so both are valid comparators. The committee noted that this treatment would not be used in any person who was not able to have trifluridine–tipiracil alone or regorafenib. So, it concluded that the comparison with best supportive care was less relevant in terms of which treatment it would likely displace at this position in the treatment pathway.

## Clinical effectiveness

### Key clinical trial: SUNLIGHT

- 3.4 The clinical evidence for trifluridine–tipiracil plus bevacizumab came from an open-label phase 3 randomised controlled trial (RCT), SUNLIGHT (n=492). It included people with unresectable, refractory mCRC who had had a maximum of 2 previous chemotherapy regimens. It evaluated trifluridine–tipiracil plus bevacizumab compared with trifluridine–tipiracil alone, and the primary outcome was OS. Other outcomes included progression-free survival (PFS), overall response rate, disease control rate, adverse events and health-related quality of life. The results showed that there was a statistically significant increase for trifluridine–tipiracil plus bevacizumab compared with trifluridine–tipiracil alone for OS (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.49 to 0.77) and PFS (HR 0.44, 95% CI 0.36 to 0.54). The clinical experts said that the estimates of OS and PFS in the trial were plausible and likely generalisable to NHS practice. They also highlighted that the rate of adverse events associated with bevacizumab in the trial was relatively low and thought that trifluridine–tipiracil plus bevacizumab is well tolerated. The committee concluded that there was a clear survival benefit of adding bevacizumab to trifluridine–tipiracil.

## Previous bevacizumab use

3.5 The company's base-case analysis used data from the intention-to-treat population in SUNLIGHT. This included a large proportion of people who had previously had bevacizumab (72%). The company thought that:

- previous bevacizumab was not a treatment effect modifier
- the intention-to-treat population in SUNLIGHT was generalisable to people with mCRC in the NHS.

But it also acknowledged that using the intention-to-treat population does not reflect clinical practice in England because bevacizumab is not currently recommended at earlier lines of mCRC treatment. The EAG agreed that the intention-to-treat population in SUNLIGHT was generalisable to people in the NHS. It pointed out that a subgroup analysis of people who had not had bevacizumab in SUNLIGHT suggested the treatment effect of trifluridine–tipiracil plus bevacizumab was potentially larger in people who had not had bevacizumab before. But this effect was not statistically significant. The clinical experts suggested that the treatment effect of trifluridine–tipiracil plus bevacizumab in SUNLIGHT may have underestimated the treatment effect in people with mCRC in the NHS. But, they thought that the size of the additional treatment effect was unquantifiable. The clinical experts also clarified that, if bevacizumab is recommended at earlier lines of treatment in the future, a clear benefit of trifluridine–tipiracil plus bevacizumab would still be seen. The committee concluded that it was appropriate to consider the SUNLIGHT intention-to-treat population regardless of previous bevacizumab use. It also concluded that, if bevacizumab is added to earlier treatment lines in future clinical practice, the SUNLIGHT treatment effects will become more generalisable to people with mCRC in NHS clinical practice.

## Indirect treatment comparison

3.6 The company did not compare trifluridine–tipiracil plus bevacizumab with regorafenib in an RCT. So, it did a network meta-analysis (NMA) to provide an indirect comparison of estimates for the relative treatment effectiveness for OS

and PFS. The results of the NMA favoured trifluridine–tipiracil plus bevacizumab compared with regorafenib for OS (HR 0.60, 95% CI 0.38 to 0.95) and PFS (HR 0.49, 95% CI 0.31 to 0.84). The EAG noted that the NMA was based on hazard ratios that assumed proportionality in hazards. The company acknowledged that this may have biased the results and associated extrapolations at certain time points. Although the EAG agreed, it also said that was unlikely to have had a significant effect on the results because long-term OS for mCRC is low. The committee thought that the proportional hazards assumption was likely to hold for OS and PFS for trifluridine–tipiracil plus bevacizumab. It concluded that the results of the NMA were appropriate for decision making.

## Economic model

### Company's modelling approach

3.7 The company presented a 3-state partitioned survival model to estimate the cost effectiveness of trifluridine–tipiracil plus bevacizumab compared with trifluridine–tipiracil alone, regorafenib and best supportive care. The 3 health states were progression free, progressed disease and death. The model had a time horizon of 15 years and a cycle length of 1 week with no half cycle correction. The committee concluded that the model structure was appropriate.

### Source of data for OS extrapolation

3.8 To estimate long-term OS for trifluridine–tipiracil plus bevacizumab and trifluridine–tipiracil alone, the company originally fitted independent parametric models to the SUNLIGHT OS data (see [section 3.4](#)). At the first committee meeting, the committee thought that there were significant uncertainties in the long-term OS extrapolation. So, it requested long-term observational data on OS for people with mCRC having trifluridine–tipiracil alone in NHS clinical practice to help resolve this uncertainty. In response to the draft guidance consultation, the company updated its base case to model OS for trifluridine–tipiracil plus bevacizumab. It did this by applying a hazard ratio from the NMA (see

section 3.6) to OS data for trifluridine–tipiracil alone from SUNLIGHT. The EAG preferred to use long-term OS data from SACT for people with mCRC having trifluridine–tipiracil alone as the reference curve. It then applied a hazard ratio from SUNLIGHT to model OS for trifluridine–tipiracil plus bevacizumab. The EAG noted that the Kaplan–Meier curves from SUNLIGHT and SACT were very similar, suggesting that the control arm of SUNLIGHT was generalisable and aligned with UK clinical practice outcomes. The company clarified that it was reasonable to use the SACT data to model OS, despite not taking this approach in its base case. The committee noted that the SACT data was an optimal source for validating OS because:

- the number of people in the dataset was very large (n=6,170)
- the data was mature, with longer-term follow up for more people at the tail of the curve
- the data came directly from NHS practice in England, so was generalisable to the target mCRC population in NHS clinical practice.

The committee concluded that survival in SUNLIGHT was similar to survival in the SACT data. But it preferred using the SACT data for trifluridine–tipiracil as the reference curve for the analysis. It also preferred to apply the hazard ratio for trifluridine–tipiracil plus bevacizumab from SUNLIGHT to model OS for the intervention.

## Chosen extrapolation method for OS

3.9 The company's base case used a log-logistic extrapolation for OS with trifluridine–tipiracil alone using SUNLIGHT data. This was because the company thought that the log-logistic extrapolation:

- had the best statistical and visual fit to the SUNLIGHT OS data
- had a projected OS at 5 years that was supported by the clinical expert opinion it had sought.

The EAG acknowledged that the estimate of people alive at 5 years in the log-logistic extrapolation was a closer statistical fit to the SACT Kaplan–Meier

curve at 5 years. But, it thought that the log-logistic extrapolation was not clinically plausible because:

- The proportion of people alive at 5 and 10 years in the log-logistic extrapolation fitted to SUNLIGHT was too high according to input from the EAG's clinical expert.
- The closer statistical match of the company's base case (the log-logistic extrapolation fitted to SUNLIGHT) to the SACT data at 5 years was because of censoring at this time point. That is, very few people were alive at 5 years, which affected the reliability of OS projections.
- When using a log-logistic extrapolation fitted to SACT data, OS benefit for trifluridine–tipiracil plus bevacizumab extended beyond the SUNLIGHT follow-up period without sufficient data to support this assumption.

The EAG preferred to use a generalised gamma extrapolation because it:

- produced a steeper decline in early survival, in line with the EAG's clinical expert opinion
- provided a closer statistical fit at 2 years to the OS data from SACT for trifluridine–tipiracil alone, and a more clinically plausible OS projection at 5 years
- tended towards having no people alive at 10 years, which was more clinically plausible in the EAG's view.

The EAG noted that the OS projections at 5 and 10 years were based on very few people. The clinical experts thought that survival of 1% of people at 5 years was clinically plausible. They thought that it was possible with current treatments that a very small proportion of people would be alive at 10 years with limited disease burden and treated metastases. But, they thought that the evidence for this was limited. The committee noted that the high quality of the SACT data reduced the uncertainty in the OS projections. It thought that, in the updated EAG's and company's base cases, both the log-logistic and generalised gamma OS extrapolations could have been plausible. The committee noted that the cost-effectiveness estimates were highly sensitive to the choice of extrapolation function. It also thought that

the differences in the tail ends of the OS extrapolation curves were the key drivers of cost-effectiveness estimates. But, it thought that, because of the size and maturity of the SACT data, any remaining uncertainty was unresolvable. The committee noted the importance of the generalised gamma distribution meeting zero in this extrapolation, and that it could have resulted in bias against trifluridine–tipiracil plus bevacizumab. This was because the hazard ratio of the intervention was applied to this reference curve. The committee thought that this approach could have been optimistic. This was because there was insufficient long-term data from SUNLIGHT to support the projected survival at 5 or 10 years in the company's extrapolation of OS. The committee thought that, ideally, the intervention should have been cost effective in both extrapolations. It agreed that the range of possible survival estimates were represented, but that generalised gamma was more of a conservative approach, and log-logistic was a more optimistic approach. The committee considered both curves in its decision making. It thought that the model that most accurately represented OS was likely to fall between the 2 extrapolations.

## Treatment waning

- 3.10 At the first meeting, the committee requested treatment waning scenarios to characterise uncertainty around duration of treatment effects. In response to the draft guidance consultation, the company updated its base case to apply a treatment waning effect to OS for trifluridine–tipiracil plus bevacizumab between 3 and 5 years. But, it highlighted that there was no evidence for a treatment waning effect in SUNLIGHT or previous appraisals. The EAG thought that the company's approach did not sufficiently account for the extended OS benefit of trifluridine–tipiracil plus bevacizumab. It preferred a scenario in which treatment waning was applied at 1 to 2 years. It highlighted that a treatment waning effect may have been appropriate for the log-logistic extrapolation (an optimistic extrapolation of OS). But, it did not think a waning effect should be applied if a generalised gamma extrapolation was preferred. At the second committee meeting, the committee thought that the changes to OS modelling and use of the SACT data (see [section 3.8](#) and [section 3.9](#)) reduced uncertainty about OS. It thought that the log-logistic curve may have been optimistic for representing the survival of people having trifluridine–tipiracil. It also thought that applying a



longer-term treatment effect to this curve could have resulted in health benefits associated with the addition of bevacizumab that were unproven. But the committee recalled that both the log-logistic and generalised gamma extrapolations of OS could have been clinically plausible. The committee preferred to consider the log-logistic scenario to be the optimistic end of the range with generalised gamma as a conservative scenario. With the evidence presented, the committee concluded that it would only be appropriate to apply a treatment waning effect if only an optimistic OS extrapolation of trifluridine–tipiracil was used. The committee recalled that OS was likely to fall between the 2 extrapolations (see section 3.9). So, it did not think that it was appropriate to have treatment waning in this circumstance. It concluded that the rationale for treatment waning was limited by the availability of new evidence and preferred analyses without treatment waning.

## Regorafenib OS and PFS

3.11 The company modelled OS and PFS for regorafenib in its base case. It originally did this by applying hazard ratios from a random-effects NMA (see [section 3.6](#)) to the OS and PFS extrapolated curves for trifluridine–tipiracil plus bevacizumab. The EAG noted that the curves used for OS and PFS were accelerated failure time models. It said that proportional hazards assumptions do not hold for this type of model. The EAG provided an additional analysis in the form of a naive comparison with regorafenib. It did this by fitting independent survival curves to the Kaplan–Meier data for regorafenib from the CORRECT study. This was a phase 3 RCT of regorafenib with best supportive care compared with placebo with best supportive care in adults who had previously had treatment for mCRC. The EAG acknowledged that neither approach was ideal. But, it thought that the naive comparison may have been less biased, so used it in its base case. The committee noted that this made minimal difference to the cost-effectiveness results. It also noted that, although the company had used accelerated failure time models as the reference curve, a hazard ratio assuming proportional hazards could reasonably be applied. The committee acknowledged that using this approach maintained randomisation across the clinical trials in the NMA. The committee thought that it would be more appropriate to:

- use trifluridine–tipiracil alone as the reference curve



- apply the hazard ratios from the random-effects NMA for regorafenib to the trifluridine–tipiracil reference curve.

In response to the draft guidance consultation, the company updated its base case to match this approach. The committee concluded that the updated approach to modelling regorafenib OS and PFS was appropriate for decision making. This was because it used the most appropriate fit for the reference curve and maintained randomisation.

## Regorafenib time on treatment

3.12 In its updated base case, the company calculated time on treatment with regorafenib by applying a hazard ratio to the PFS curve. This was based on the ratio of median time on treatment (1.7 months) to median PFS (1.9 months) from CORRECT. It resulted in a proportion of 89.4% of people on regorafenib being progression free. The EAG disagreed with this approach, stating that it overestimated the mean time on treatment and the acquisition costs of regorafenib. The EAG preferred to assume in its base case that:

- a proportion of people who were progression free at any one time were having regorafenib
- the proportion who were progression free and having regorafenib was equal to mean time on treatment from CORRECT divided by the mean modelled PFS from the company's base-case analysis.

The EAG highlighted that its base-case approach resulted in a closer replication of both the mean and median time on treatment for regorafenib in CORRECT than the company's approach. It also thought that an approach to treatment acquisition costs based on means rather than medians was more methodologically appropriate. The company indicated that the EAG's approach underestimated the proportion of the progression-free cohort on regorafenib treatment. It also explained that the shape of the resulting curve was visually implausible. This was because it assumed that a proportion of the cohort never had treatment with regorafenib. But, the EAG pointed out that the shape of the curve in its proportional approach was not a key driver

of cost-effectiveness estimates. This was because time on treatment was short, so not affected by discounting. The EAG provided an additional scenario that fitted an exponential curve to the median time on treatment in CORRECT. It thought that this addressed the concerns about the shape of the curve, but gave similar results to the proportional approach. The committee concluded that either of the EAG's approaches (that is, the proportional approach or exponential curve applied to the median time on treatment) was appropriate. It considered the range of cost-effectiveness estimates based on these preferred assumptions.

## Regorafenib relative dose intensity

3.13 The company modelled regorafenib's relative dose intensity (RDI) as equal to that of trifluridine–tipiracil. This was in line with the preferred approach in [NICE's technology appraisal guidance on regorafenib for previously treated mCRC](#). The company highlighted that the outcomes in the regorafenib and trifluridine–tipiracil arms of its revised base case were similar, which suggested that similar RDI was a reasonable assumption. The EAG preferred to use data from CORRECT to reflect RDI, which was consistent with the preferred data source for PFS and time on treatment for regorafenib. The clinical experts noted that side effects with regorafenib would be managed with dose reductions in clinical trials and NHS practice. But, they thought that continuing with the full dose would be possible despite the side effects if the mCRC was responsive to the full dose of regorafenib. They thought that benefit was still possible in terms of PFS with lower doses of regorafenib. The committee noted that the differences between the company's and EAG's assumptions for regorafenib's RDI had a minimal impact on cost-effectiveness estimates. But, in principle, it preferred an analysis that more closely matched regorafenib's use in clinical practice, which likely includes dose reductions in line with CORRECT.

## Treatment-specific utilities

3.14 In the company's base case (see [section 3.7](#)), utility values for the progression-free and progressed health states were derived from a regression model fitted to

EQ-5D data from SUNLIGHT (see [section 3.4](#)). The company thought that treatment-specific utilities, in which higher utility values were assigned to trifluridine–tipiracil plus bevacizumab, were appropriate. This was based on a higher overall response rate compared with trifluridine–tipiracil alone. In response to the draft guidance consultation, the company updated its base case to include utility waning. It did this by applying a temporary utility increment (for 3 months) to people entering the progressed-disease health state. The increment was based on a utility regression model in SUNLIGHT. The company justified this approach by highlighting the increased time to deterioration in quality of life after disease progression in the trifluridine–tipiracil plus bevacizumab arm of SUNLIGHT. But, the EAG pointed out that:

- this increased time to deterioration was also seen in the trifluridine–tipiracil monotherapy arm
- the quality-of-life benefit was already captured in the model through the additional utility gains from extended PFS
- the interaction terms for the treatment arm and progression state were not statistically significant
- the treatment effect was not statistically significant when adjusted for baseline utility.

The EAG preferred pooled utility values for the progression-free and progressed health states. The committee agreed that the evidence for treatment-specific utility values and the utility waning approach was not convincing. It preferred pooled utility values for each health state.

## Source of utility values

- 3.15 The EAG highlighted that the cost-effectiveness results were sensitive to the source of utility values because of their impact on the severity weighting applied. It used utility values from SUNLIGHT in its base case. But, it also provided sensitivity analyses with utility values that were used in previous NICE technology appraisals in mCRC. These came from a variety of sources, including CORRECT, CONCUR (a regorafenib clinical trial) and an additional study on cetuximab in

first-line mCRC. For the progression-free health state, the utility values ranged from 0.72 to 0.76, and for the progressed health state the utility values ranged from 0.59 to 0.68. The committee considered that:

- Most of the available utility estimates were in the appropriate populations (apart from cetuximab used in a first-line setting).
- Each source of utility evidence may have had individual uncertainties and level of quality, for example, small numbers of EQ-5D observations for people with progressed cancer, or differences in the time point of when the observations were recorded.
- Some observations of the data were inconsistent with each other. For example, the utility decrements associated with disease progression were considerably higher in the values sourced from CORRECT.
- The most methodologically appropriate approach might be to pool all available utility value estimates for later line mCRC utility estimates to create the best available evidence.

The committee noted that the midpoint value of all the available utility evidence was about 0.64 for the progressed-disease health state. The utility values used in [NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC](#) were methodologically less appropriate because they used values from a first-line cetuximab study. But they likely resulted in values similar to the midpoint utility values that could be expected if the values were formally pooled. It noted that these estimates would approximately maintain the quality-of-life utility progression decrement seen in SUNLIGHT. At the same time, they would potentially provide more accurate estimates of the absolute quality of life needed for the severity modifier calculation than SUNLIGHT alone. The committee considered the range of all the available estimates, including the plausibility of the decrement in utility at progression. It acknowledged the sensitivity of the severity modifier calculation to the source of utility values. On balance, the committee concluded that a formal pooling of all available utility evidence would be most appropriate. But, in the absence of this data, the utility values from NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC were likely to approximate the expected pooled utility estimates.

## Costs of subsequent treatments

3.16 In the company's base case, the costs of subsequent treatments were modelled using the proportion and distribution of subsequent treatments used in SUNLIGHT (see [section 3.4](#)). The EAG highlighted that the combinations of subsequent treatments in SUNLIGHT do not match UK clinical practice. It also noted that the high proportion of retreatment with regorafenib seen in SUNLIGHT would be unlikely in NHS practice. The EAG used the same proportion of people having subsequent treatments as in SUNLIGHT (58.3%). But, it preferred to assume that, based on expected NHS clinical practice, everyone:

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

The EAG also highlighted that increased PFS with more effective treatments may have increased the chance of people being well enough to have another line of treatment. But, it noted that the differences in subsequent treatments used across treatment arms in SUNLIGHT were small, and the impact of subsequent treatment distribution on cost-effectiveness estimates was minimal. The Cancer Drugs Fund clinical lead provided data on trifluridine–tipiracil and regorafenib treatment use at third and fourth lines in NHS England. They highlighted that the attrition rate between third- and fourth-line treatment is around 35%. The clinical experts said that differences in individual performance status and patient choice may affect treatment sequencing. They also said that improved survival may lead to increased use of subsequent treatments. But, the committee noted uncertainty about subsequent treatments because there was no data on how improved survival with trifluridine–tipiracil with bevacizumab would affect these proportions. It thought that this may have led to bias in favour of trifluridine–tipiracil with bevacizumab. After the draft guidance consultation, the company updated its base case so that 35% of people had subsequent treatment, in line with the EAG's treatment distributions. The committee concluded that this updated approach was appropriate for decision making.

## Costs of bevacizumab administration

3.17 In response to the draft guidance consultation, a consultee raised an issue relating to the administration costs of bevacizumab. The company's and EAG's base cases both used an administration cost of £286.71, applied every 2 weeks. This corresponds to the Healthcare Resource Group (HRG) code SB12Z: deliver simple parenteral chemotherapy. The EAG was concerned that the subsequent administrations of each 28-day treatment cycle may not have represented the costs paid in the NHS. It presented a scenario using a cost of £158.50 for the subsequent administrations. This corresponded to the outpatient care code WF01A (non-admitted nurse-led face-to-face medical oncology service) of the [2021/22 National Schedule of NHS Costs](#). The Cancer Drugs Fund clinical lead explained that the HRG codes used for bevacizumab administration vary between NHS trusts. They thought that the following HRG code combinations could be likely approaches to costing each cycle of bevacizumab treatment:

- HRG codes SB12Z for day 1 and SB15Z (delivery of a subsequent element of a chemotherapy cycle) for day 15 for each cycle, which would give a total cost of £655.15 (2021/22 reference costs), or
- HRG code SB17Z (delivery of chemotherapy which is not on the national list) for day 1 and day 15 of each cycle, which would give a total cost of £804.90 (2021/22 reference costs).

The Cancer Drugs Fund lead suggested that using the midpoint of the costs of the 2 HRG approaches would be reasonable. The committee noted that, when adjusted for RDI, the midpoint cost of bevacizumab administration per cycle was close to the cost used in the company's and EAG's base cases. It concluded that this midpoint approach (using 2021/22 NHS reference costs in line with [section 4.4.9 of NICE's health technology evaluations manual](#)) was the most appropriate way to include the costs of bevacizumab administration.

## Severity

3.18 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in NHS). The committee

may apply a greater weight (a severity modifier) to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity. In both the company's and the EAG's updated base cases, the QALYs generated from the company model implied a 1.2 weighting for the comparisons with both trifluridine–tipiracil alone and regorafenib. Additional analyses from the EAG highlighted that the appropriate severity weighting implied by the QALY shortfall calculations was sensitive to:

- the OS extrapolation used (see [section 3.9](#))
- the utility values used (see [section 3.14](#) and [section 3.15](#)).

The committee preferred to use a starting age of 65 years from the SACT data and sex distribution from SUNLIGHT in the severity modifier calculations. It considered the range of plausible proportional QALY shortfall based on the results of these calculations. The committee thought that there was a high degree of certainty in the model starting age and OS modelling from using the SACT data (see [section 3.8](#) and [section 3.9](#)). This meant that most of the remaining uncertainty came from the choice of utility values. But, the committee thought that the exact quantitative estimates of QALY shortfall were likely to be an accurate representation of proportional QALY shortfall in mCRC. Using the committee's preferred assumptions (see [section 3.21](#)), the proportional QALY shortfall value resulted in a severity weighting of 1.2. But, the committee noted that small changes in some assumptions could have resulted in a 1.7 QALY weighting. The committee explored alternative assumptions and considered each severity modifier for a given scenario, noting the relevant severity modifier was highly dependent on choice of OS extrapolation (see [section 3.9](#)).

## Other considerations

### Equalities

- 3.19 At consultation, a potential equality concern was raised about differential response to treatment between ethnic groups. The committee thought that there was no available evidence indicating that ethnicity was a treatment modifier. It



also thought that any recommendation would not restrict access to treatment for some people over others based on ethnicity. So, the committee agreed that this did not represent an equalities issue. The committee concluded that no equality issues were raised that would have an impact on its decision making about the treatment of mCRC with trifluridine–tipiracil plus bevacizumab.

## Cost-effectiveness estimates

### Acceptable incremental cost-effectiveness ratio

3.20 [NICE's health technology evaluations manual](#) notes that, above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee noted that the current ICER calculation did not consider the potential that the benefit of trifluridine–tipiracil plus bevacizumab was underestimated. This was because the relative treatment effect from SUNLIGHT was established in a bevacizumab pretreated population (see [section 3.5](#)). The committee thought that using a large real-world UK dataset to inform both OS modelling and the age used in the severity modifier calculations substantially reduced the uncertainty in the cost-effectiveness estimates (see [section 3.8](#)). Considering both these points, the committee concluded that an acceptable ICER would be up to £30,000 per QALY gained.

### Committee's preferred assumptions

3.21 The committee considered the results of the cost-effectiveness analysis for trifluridine–tipiracil using its preferred assumptions, which included:

- using data from SACT to model OS for trifluridine–tipiracil alone and applying hazard ratios to this data to model OS for trifluridine–tipiracil plus bevacizumab from SUNLIGHT and regorafenib from the NMA (see [section 3.8](#) and [section 3.11](#))
- considering a range of cost-effectiveness estimates from both the log-



logistic and generalised gamma scenarios, with the model that most accurately represented OS likely to fall between the 2 extrapolations (see [section 3.9](#))

- modelling regorafenib time on treatment using either a proportional approach based on means from CORRECT or an exponential approach applied to CORRECT median time on treatment (see [section 3.12](#))
- using the regorafenib RDI in line with CORRECT (see [section 3.13](#))
- pooled treatment utilities based on the midpoint values of all of the available utility evidence, with the utility values from [NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC](#) used as approximations (see [section 3.14](#) and [section 3.15](#))
- assuming 35% of people have subsequent treatment, with treatment distributions in line with the EAG's assumptions (see [section 3.16](#))
- using the midpoint value from the Cancer Drugs Fund lead's 2 suggested approaches for bevacizumab administration costs (see [section 3.17](#))
- using a severity weighting of 1.2, while considering alternative scenarios with a 1.2 or 1.7 severity weighting depending on the quantitative results of QALY shortfall calculations (see [section 3.18](#)).

The exact cost-effectiveness results cannot be reported here because of confidential discounts for trifluridine–tipiracil, comparators and subsequent treatments. The company's base-case ICERs were below £30,000 per QALY gained, regardless of the weighting applied. The EAG's base-case ICERs were below £30,000 per QALY gained compared with:

- trifluridine–tipiracil alone using the 1.2 and 1.7 QALY weightings
- regorafenib using a 1.7 weighting only.

The committee considered a range of ICERs for trifluridine–tipiracil plus bevacizumab. With its preferred assumption and a 1.2 severity weighting, the cost-effectiveness results compared with trifluridine–tipiracil alone and with regorafenib were within the range that NICE normally considers an acceptable use of NHS resources.

## Conclusion

### Recommendation

- 3.22 The committee concluded that the most plausible ICERs based on its preferred assumptions are likely to represent a cost-effective use of NHS resources. So, trifluridine–tipiracil plus bevacizumab is recommended within its marketing authorisation for treating mCRC.

## 4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has metastatic colorectal cancer and the healthcare professional responsible for their care thinks that trifluridine–tipiracil plus bevacizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

# 5 Evaluation committee members and NICE project team

## Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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

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

## Chairs

### **Charles Crawley and Baljit Singh**

Chair and vice chair, technology appraisal committee B

## NICE project team

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

### **Emma McCarthy and Michael Bell**

Technical leads

### **Adam Brooke**

Technical adviser

### **Jeremy Powell**

Project manager

**Emily Crowe**

Associate director

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