NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

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

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

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

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

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

Issue date: June 2024

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using trifluridine–tipiracil plus bevacizumab in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 27 June 2024
- Second evaluation committee meeting: 11 July 2024
- Details of membership of the evaluation committee are given in section 5.

1 Recommendations

1.1 Trifluridine–tipiracil with bevacizumab is not 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, anti-vascular endothelial growth factor or anti-epidermal growth factor receptor treatments).

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

Why the committee made these recommendations

Standard treatment for metastatic colorectal cancer after 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 similar benefits for trifluridine–tipiracil plus bevacizumab compared with regorafenib.

The cost-effectiveness estimates are uncertain because of assumptions used in the economic model about how long people live on trifluridine–tipiracil plus bevacizumab and trifluridine–tipiracil alone. So, further analysis is needed, and trifluridine–tipiracil plus bevacizumab is not 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 per 20-tablet pack and £1,500 per 60-tablet pack (excluding VAT; BNF accessed May 2024). The list price of trifluridine–tipiracil (20 mg/8.19 mg) is £666.67 per 20-tablet pack and £2,000 per 60-tablet pack. (excluding VAT; BNF accessed May 2024).

2.4 The list price of bevacizumab (25 mg/ml) varies between £205.00 and £242.66 per 4-ml vial, and between £810.00 and £924.40 per 16-ml vial (excluding VAT; BNF accessed May 2024).

2.5 The company has a commercial arrangement. This makes trifluridine–tipiracil available to the NHS with a discount, and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence.

2.6 There is a discount for bevacizumab agreed with the Commercial Medicines Unit. 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. See the committee papers for full details of the evidence.

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 are diagnosed and have treatment at earlier stages of the condition. They also noted that the ability to diagnose and treat as early as possible may vary across NHS trusts. This can result in a postcode lottery for 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 600, RAS wild-type, and microsatellite instability/mismatch repair deficiency. When these molecular markers are present, specific biologicals 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 use in combination of previous chemotherapy agents. 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 clinical practice in the NHS because of differences in treatment combinations given earlier in the pathway.

Comparators

3.3 The company's proposed comparators were narrower 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 for people with mCRC is an important consideration. They added that the choice of regorafenib or trifluridine–tipiracil alone may be affected by the person's current performance status and 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 that was not able to have trifluridine–tipiracil alone or regorafenib. So, it thought 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, 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 overall survival. Other outcomes included progression-free survival, 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 overall survival (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.49 to 0.77) and progression-free survival (HR 0.44, 95% CI 0.36 to 0.54). The clinical experts said that the estimates of overall and progression-free survival in the trial were plausible and were likely generalisable to NHS practice. They also highlighted that the rate of adverse events associated with bevacizumab in the trial was relatively low and considered 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 highlighted that, although this does not reflect clinical practice in England because bevacizumab is not currently recommended at earlier lines of mCRC treatment, it 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.

The EAG agreed that the ITT population in SUNLIGHT was generalisable to people in the NHS. It pointed out that although a subgroup analysis of people who had not had bevacizumab in SUNLIGHT suggested the treatment effect of trifluridine–tipiracil plus bevacizumab in SUNLIGHT was potentially larger in people who had not had bevacizumab before, 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 have direct clinical-effectiveness evidence for trifluridine–tipiracil plus bevacizumab compared with regorafenib or best supportive care. So, it did a network meta-analysis (NMA) to provide estimates of relative treatment effectiveness for overall and progression-free survival. The results of the NMA favoured trifluridine–tipiracil plus bevacizumab compared with regorafenib for overall survival (HR 0.60, 95% CI 0.38 to 0.95) and progression-free survival (HR 0.49, 95% CI 0.31 to 0.84). The EAG noted that the NMA was based on reported HRs 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 stated that was unlikely to have had a significant effect on the results because long-term overall survival for mCRC is low. The committee thought that the proportional hazards assumption was likely to hold for overall and progression-free survival 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.

Overall survival extrapolation of trifluridine–tipiracil plus bevacizumab and trifluridine–tipiracil alone

3.8 To estimate long-term overall survival for trifluridine–tipiracil plus bevacizumab and trifluridine–tipiracil alone, the company fitted independent parametric models to the SUNLIGHT overall survival data (see section 3.4). The company's base case used a log-logistic extrapolation because the company thought that the log-logistic function:

- had the best statistical and visual fit to the data
- was supported by the clinical expert opinion it had sought.

The EAG did not think that the log-logistic extrapolation was clinically plausible because:

- the proportion of people alive at 5 years was too high, according to input from its clinical expert
- the modelled overall survival increase for trifluridine–tipiracil plus bevacizumab compared with trifluridine–tipiracil alone at year 2 was greater than the overall survival benefit reported in SUNLIGHT at 1 year.

The EAG preferred to use a generalised gamma extrapolation because it produces a steeper decline in early survival, in line with clinical expert opinion. It noted that the overall survival curves for trifluridine–tipiracil plus bevacizumab and trifluridine–tipiracil alone crossed over at 4 years in the generalised gamma model. But the EAG highlighted that the number of people predicted to still be alive at this point was extremely small. This meant the curves crossing over had a minimal impact on the modelled outputs. The clinical experts commented that both the company's and EAG's overall survival curves could have potentially underestimated overall survival for trifluridine–tipiracil alone. But, they noted that this prediction was based on limited data from their own clinical practice. The committee considered that log-logistic and generalised gamma

extrapolations could be plausible, but both were uncertain. It also thought that the differences in the tail ends of the extrapolation curves were the key drivers of cost-effectiveness estimates. It considered that it would be appropriate to consider analyses applying relative treatment effects from SUNLIGHT to observational survival data for trifluridine–tipiracil alone. This was because the proportional hazards assumption was likely to hold (see section 3.6). It concluded that, because of the important uncertainties in the overall survival modelling, additional analyses in which a hazard ratio from SUNLIGHT (see section 3.4) is applied to long-term survival data from UK clinical practice were needed to help resolve this uncertainty.

Regorafenib overall and progression-free survival

3.9 The company modelled overall and progression-free survival for regorafenib in its base case. It did this by applying HRs from a random-effects NMA (see section 3.6) to the overall and progression-free survival extrapolated curves for trifluridine–tipiracil plus bevacizumab. The EAG noted that the curves used for overall and progression-free survival were accelerated failure time models. It stated 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 randomised controlled trial 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 considered 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 concluded that it might prefer the

company's approach because it maintained randomisation. But, the committee also noted that using trifluridine–tipiracil plus bevacizumab as the reference curve meant that exploring treatment waning scenarios in the model would require artificial upwards adjustment of the hazard ratios of the comparator arms and may not represent a true waning effect. The committee thought that it would be more appropriate to use trifluridine–tipiracil alone as the reference curve, and apply the hazard ratios from the random-effects NMA for regorafenib to that curve. It concluded that additional analyses using this approach were needed, including exploration of treatment-waning scenarios, to provide more certainty when validating overall survival.

Regorafenib time on treatment

3.10 The company assumed that time on treatment for regorafenib was equal to progression-free survival for regorafenib in the company's base case. This was in line with the approach used in NICE's technology appraisal guidance on regorafenib for previously treated mCRC, in which people had regorafenib treatment until their cancer progressed. The EAG disagreed with this approach, stating that it overestimated the acquisition costs of treatment with regorafenib. The EAG's clinical expert stated that regorafenib treatment could be stopped before disease progression because of toxicity. The clinical experts confirmed that regorafenib can be stopped before progression because of tolerability issues. The EAG preferred to assume 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 progression-free survival from the company's base-case analysis.

The EAG highlighted that this approach (in which a proportion of people who were progression-free were having regorafenib) resulted in a closer median time on treatment for regorafenib (median 8.8 weeks) to that seen in CORRECT (median 7.4 weeks) than the company's approach (median 14.0 weeks). The EAG calculated the proportion of the progression-free cohort on regorafenib treatment to be 68%, and the company considered that this was an underestimate. The EAG agreed to check its approach. The committee agreed that time on treatment with regorafenib would be overestimated if treatment was assumed until progression. But, it also acknowledged that the scenario provided by the EAG could have been an underestimate. It concluded that it would like to see further sensitivity analysis that increased the proportion of the progression-free cohort on regorafenib.

Regorafenib relative dose intensity

3.11 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 EAG preferred to use data from CORRECT to reflect RDI, which was consistent with the preferred data source for progression-free survival, overall survival 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 considered that benefit was still possible in terms of progression-free survival with lower doses of regorafenib. The committee considered that the differences between the company's and EAG's assumptions for 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.

Utility values

3.12 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 assigned higher utility values for trifluridine–tipiracil plus bevacizumab. This was based on a higher overall response rate compared with trifluridine–tipiracil alone. The EAG noted that the interaction terms for the treatment arm and progression state were not statistically significant. It also noted that, when adjusted for baseline utility value, the treatment effect was no longer statistically significant. It preferred pooled utility values for the progression-free and progressed health states. It also provided additional scenarios with alternative sources of utility values from NICE's technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC and NICE's technology appraisal guidance on regorafenib for previously treated mCRC. The committee agreed that the evidence for treatment-specific utility values was not convincing, and preferred pooled utility values for each health state. It considered the range of utility value sources, but noted that the source of pooled utility values had limited impact on the cost-effectiveness results.

Costs of subsequent treatments

3.13 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 UK 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 progression-free survival 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 currently 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. The committee concluded that using the proportion of people having subsequent treatment data from NHS England was appropriate for decision making. But, it noted uncertainty 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.

Severity

3.14 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. The company and EAG agreed that the QALYs generated from the company's and EAG's models implied:

- a 1.2 QALY weighting for the comparison with trifluridine–tipiracil alone
- a 1.7 QALY weighting for the comparison with regorafenib.

The company also pointed out that the data from NICE's technology appraisal guidance on trifluridine–tipiracil alone for previously treated mCRC gave a 1.7 weighting when used to calculate QALY shortfall. The committee recalled that the clinical experts considered overall survival extrapolations may have underestimated the clinical effectiveness (and therefore overall survival) of trifluridine–tipiracil alone (see section 3.8). They considered that the size of the QALY shortfall calculated for the trifluridine–tipiracil alone may have been overestimated if that were the case. The committee also thought that the model starting age of 62 years (informed by the mean age in SUNLIGHT) used to calculate QALY shortfall may not reflect average age of people with mCRC in NHS practice. The patient experts explained that the number of younger people with mCRC has increased over time. The clinical experts stated that there has also been an increase in the number of older people with mCRC suitable for active treatment. They thought that the average age of people having treatment is higher in clinical practice than it was in the clinical trial, likely between 65 and 70 years. The committee considered that it would like further data on the mean age of people having trifluridine–tipiracil alone for mCRC in current NHS practice. Also, it would like to see more data on survival with trifluridine–tipiracil alone. The committee concluded that some uncertainty with the decision on which QALY weighting was most appropriate for people with mCRC in the comparison with trifluridine–tipiracil alone could be resolved through:

- observational data on the mean age of people starting treatment with trifluridine–tipiracil alone
- overall survival estimates for people with mCRC taking trifluridine tipiracil alone.

Other considerations

Equalities

3.15 No equalities concerns were raised by the stakeholders. Also, the committee did not consider that there were any equality issues that would have an impact on its decision making about treatment of mCRC with trifluridine–tipiracil plus bevacizumab.

Cost-effectiveness estimates

Committee's preferred assumptions

3.16 The exact cost-effectiveness results cannot be reported here because of confidential discounts for trifluridine–tipiracil, comparators and follow-up treatments. The company's base-case incremental cost-effectiveness ratios (ICERs) were above the range that NICE considers an acceptable use of NHS resources at a QALY weighting of 1 and 1.2, and within the standard cost-effectiveness range with a 1.7 QALY weighting. The EAG's base-case ICERs were above the range regardless of the QALY weighting applied. The committee recalled the considerable uncertainty around some of the model assumptions in the company's base case, especially in:

- the overall survival extrapolations for trifluridine–tipiracil alone and trifluridine–tipiracil plus bevacizumab (see section 3.8)
- the QALY shortfall calculations informing the severity modifier (see section 3.14).

Because of this uncertainty, the committee considered that further analysis that represented its preferred assumptions was needed to inform decision making. But, it noted that, with the current preferred assumptions and uncertainty, the ICERs were more than what NICE normally considers

a cost-effective use of NHS resources. The committee requested the following further analyses:

- observational data to validate overall survival for trifluridine–tipiracil alone in UK practice, and modelling of trifluridine–tipiracil plus bevacizumab overall survival by applying the SUNLIGHT overall survival hazard ratio to this data (see section 3.8)
- data on the mean age of people having trifluridine–tipiracil alone for mCRC in current UK practice (see section 3.14)
- updated QALY shortfall calculations for trifluridine–tipiracil alone that reflect the further analyses, particularly overall survival and mean age (see section 3.14)
- analyses in which regorafenib survival estimates are modelled by applying hazard ratios from the NMA to the curve for trifluridine–tipiracil alone (see section 3.9)
- analyses in which regorafenib time on treatment is modelled as a higher proportion of people in the progression-free state than in the EAG's base case (see section 3.10)
- sensitivity analyses in which the treatment effect on survival with the intervention and comparators wanes over time (see section 3.9).

Conclusion

Recommendations

3.17 The committee took into account its preferred assumptions, and the key uncertainties in overall survival modelling and QALY shortfall calculations informing the severity modifier. It concluded that trifluridine–tipiracil plus bevacizumab is unlikely to represent a cost-effective use of NHS resources, and that further analyses were needed to inform decision making. So, it could not recommend trifluridine–tipiracil plus bevacizumab for treating mCRC after 2 systemic treatments.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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

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

Chair

Baljit Singh

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, Michael Bell

Technical leads

Adam Brooke

Technical adviser

Jeremy Powell

Project manager

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