NATIONAL

INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer

1 Recommendations

1.1 Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy can be used as an option to treat metastatic colorectal carcinoma in adults:

- as first- or second-line treatment only, when
- targeted treatments or immunotherapy are unsuitable, and
- chemotherapy would otherwise be offered.

Bevacizumab with fluoropyrimidine-based chemotherapy can only be used if the companies have an agreed price within the Medicines Procurement and Supply Chain.

1.2 This recommendation is not intended to affect treatment with bevacizumab with fluoropyrimidine-based chemotherapy 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.

What this means in practice

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy must be funded in the NHS in England for the condition and

Issue date: November 2025

population in the recommendations, if it is considered the most suitable treatment option. Bevacizumab with fluoropyrimidine-based chemotherapy must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that bevacizumab with fluoropyrimidine-based chemotherapy provides benefits and value for money, so it can be used routinely across the NHS in this population.

Why the committee made these recommendations

For this evaluation, bevacizumab (originator and biosimilars) plus fluoropyrimidine-based chemotherapy was considered only for the first- and second-line treatment of metastatic colorectal carcinoma when targeted treatments or immunotherapy are not suitable, and chemotherapy alone would otherwise be offered. This does not include the whole population it is licensed for.

Usual first- and second-line treatment for metastatic colorectal cancer when targeted treatments or immunotherapy are not suitable is fluoropyrimidine-based chemotherapy alone. Bevacizumab would be used as well as chemotherapy.

Clinical trial evidence shows that bevacizumab plus chemotherapy increases how long people have before their cancer gets worse and how long they live compared with placebo plus chemotherapy.

The economic model has uncertainties because of the assumptions used. But when considering the condition’s severity, and its effect on quality and length of life, the cost-effectiveness estimates are within the range NICE considers an acceptable use of NHS resources. So, bevacizumab (originator or biosimilars) with fluoropyrimidine-based chemotherapy can be used.

2 Information about bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy

Marketing authorisation indication

2.1 Bevacizumab (Avastin, Roche [originator] and biosimilars) with fluoropyrimidine-based chemotherapy is indicated for the 'treatment of adult patients with metastatic carcinoma of the colon or rectum'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for bevacizumab (originator) in combination with fluoropyrimidine-based chemotherapy.

Price

2.3 The list price for bevacizumab (originator) for a 100-mg vial is £242.66, and a 400-mg vial is £924.40. The list price of biosimilars range from £202.50 to £242.66 for a 100-mg vial and from £810.00 to £924.40 for a 400-mg vial (excluding VAT; BNF online, accessed November 2025).

2.4 Nationally available price reductions for bevacizumab (originator and biosimilars) have been agreed with the Medicines Procurement and Supply Chain. The prices agreed through the framework are commercial in confidence.

Carbon Reduction Plan

2.5 A Carbon Reduction Plan for UK carbon emissions is not included because there are multiple companies that manufacture bevacizumab.

3 Committee discussion

The evaluation committee considered evidence submitted by the external assessment group (EAG). See the committee papers for full details of the evidence.

Pilot of a streamlined review of originator and biosimilar

3.1 The Government's 10 Year Health Plan empowers NICE to move from a static to a dynamic assessment, reviewing its guidance and helping the NHS maximise the health benefit for every pound spent through a 'whole lifecycle approach'. As part of this, methods and processes are being reviewed and developed to evaluate biosimilars when NICE did not recommend the originator, and biosimilar availability and competition has reduced the price of the technology. NICE has not previously recommended bevacizumab for treating metastatic colorectal cancer; see:

- NICE technology appraisal guidance on bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118)
- NICE technology appraisal guidance on bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer (TA212)
- NICE technology appraisal guidance on cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy (TA242).

Because of the demand for a new evaluation of bevacizumab from stakeholders, this topic was selected for this pilot. NICE developed the pilot as a faster alternative to the standard multiple technology appraisal process, which was streamlined as follows:

- The scope included a narrower population than that covered by the marketing authorisation for bevacizumab with fluoropyrimidine-based chemotherapy. That is, metastatic colorectal cancer (mCRC) when targeted therapies or immunotherapies are not suitable, when chemotherapy alone would otherwise be offered.
- The process did not include company or stakeholder submissions, and there was no technical engagement phase.

The EAG evaluated the cost effectiveness of bevacizumab (originator

and biosimilars; from here, bevacizumab) using efficient and resource-conscious methods. The EAG made the following key methodological simplifications:

- No new systematic reviews were done; instead the EAG reviewed previous technology appraisal submissions and consulted with clinical experts to identify relevant new data (see section 3.5).
- The EAG extracted key clinical data, with a reduced level of critical appraisal than for a standard technology appraisal.
- The EAG developed a new model using simplifying assumptions (see section 3.8).

The committee noted that this evaluation was a pilot of a new, pragmatic approach designed to support decision making using simplified methods and assumptions specifically for reviewing NICE guidance when biosimilar products become available. It concluded it would make its decision in this context.

Clinical management

Treatment pathway and positioning of bevacizumab

3.2 mCRC is a tumour arising from the lining of the large intestine (colon and rectum) that has spread beyond the large intestine, most often to the liver, lungs or peritoneum. The aim of treatment for mCRC is to prolong survival and improve quality of life. There are targeted treatment options and immunotherapies for mCRC, which include:

- First line:
  - pembrolizumab (see the NICE technology appraisal guidance on pembrolizumab for untreated mCRC with high microsatellite instability or mismatch repair deficiency)
  - cetuximab and panitumumab (see the NICE technology appraisal guidance on cetuximab and panitumumab for previously untreated mCRC)

  - nivolumab plus ipilimumab (see the NICE technology appraisal guidance on nivolumab plus ipilimumab for untreated unresectable or mCRC with high microsatellite instability or mismatch repair deficiency)

- Second line:
  - encorafenib plus cetuximab (see the NICE technology appraisal guidance on encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive mCRC)
  - nivolumab with ipilimumab (see the NICE technology appraisal guidance on nivolumab with ipilimumab for previously treated mCRC with high microsatellite instability or mismatch repair deficiency)
  - pembrolizumab (see the NICE technology appraisal guidance on pembrolizumab for previously treated endometrial, biliary, colorectal, gastric or small intestine cancer with high microsatellite instability or mismatch repair deficiency)
- Third line and later:
  - trifluridine–tipiracil with bevacizumab (see the NICE technology appraisal guidance on trifluridine–tipiracil with bevacizumab for treating mCRC after 2 systemic treatments; TA1008)
  - trifluridine–tipiracil alone (see the NICE technology appraisal guidance on trifluridine–tipiracil for previously treated mCRC)
  - regorafenib (see the NICE technology appraisal guidance on regorafenib for previously treated mCRC)
  - fruquintinib (see the NICE technology appraisal guidance on fruquintinib for previously treated metastatic colorectal cancer).

The choice of first- or second-line targeted therapy or immunotherapy depends on the presence or absence of 3 molecular markers: BRAF 600, RAS wild type, and microsatellite instability or mismatch repair deficiency. If targeted treatments are not suitable, fluoropyrimidine-based chemotherapy is usually offered as first- or second-line treatment (see NICE's guideline on colorectal cancer).

The EAG noted that bevacizumab could be added on to chemotherapy that is currently used as a first- or second-line treatment option.

The EAG's assessment focused on 2 populations:

- people with untreated metastatic carcinoma of the colon or rectum who would be offered fluoropyrimidine-based chemotherapy, and
- people with metastatic carcinoma of the colon or rectum who have previously had fluoropyrimidine-based chemotherapy and would be offered second-line fluoropyrimidine-based chemotherapy.

The committee noted the NICE scope restricted the population (at first and second line) to people for whom targeted treatments or immunotherapy are not suitable, and to whom chemotherapy would otherwise be offered. This did not include everyone who bevacizumab is licensed for (see section 2.1). The clinical experts stated that adding bevacizumab to chemotherapy gave additional clinical benefit. The patient expert noted that bevacizumab has the ability to shrink tumours to make surgery viable for people whose tumours were previously inoperable. They described this as having a significant impact on their overall outcome. The committee concluded that people currently having chemotherapy as a first- or second-line treatment for mCRC would welcome a new treatment option.

Subgroups based on molecular markers

3.3 The EAG did not specifically assess the RAS wild type, BRAF V600 mutation, or microsatellite instability or mismatch repair molecular marker subgroups, which have targeted treatment options. The patient experts highlighted the importance of considering the KRAS mutation status in mCRC and noted that bevacizumab has been seen as an advantageous treatment in this subgroup. The committee noted that some people in

these groups would be having chemotherapy rather than targeted treatments. In particular:

- KRAS mutation: people would be having chemotherapy at first or second line because there are no NICE-recommended first- or second-line targeted treatments for tumours with this mutation.
- RAS wild type: cetuximab or panitumumab are the only first-line treatment options. Furthermore, the clinical experts explained that people with right-sided tumours may be having chemotherapy and so bevacizumab may be beneficial in the first-line setting. This is because cetuximab and panitumumab do not appear to be beneficial for right-sided tumours.
- BRAF 600 mutation: people may be having first-line chemotherapy because encorafenib plus cetuximab is only recommended as a second-line treatment.
- Microsatellite instability or mismatch repair: there may be people who have chemotherapy after initial immunotherapy, because immunotherapy can only be used once in the treatment pathway. This would be a small number because of the rarity of this subgroup and because most people in this subgroup (approximately 60% to 70%) do not appear to have disease progression after first-line immunotherapy.

The committee acknowledged that the EAG's analysis focused on people without known mutations, who make up most people with mCRC. A clinical expert highlighted that mCRC was not routinely tested for molecular markers in the studies reviewed by the EAG, because they were older. This meant that although not specifically identified, people with these molecular markers may have been included in the trials. The clinical experts noted that prognosis differs across the subgroups based on molecular markers, but they expected a benefit of bevacizumab added on to chemotherapy across all groups. The clinical experts noted that even if data was available, subgroup analyses would be difficult because the small number of people (only 5% to 10% of

people with mCRC) have BRAF 600 mutations, microsatellite instability or mismatch repair. The committee concluded that it would appraise bevacizumab as an add on to fluoropyrimidine-based chemotherapy for first- and second-line treatment of mCRC, when targeted treatments and immunotherapy are not suitable and chemotherapy would otherwise be offered. This evaluation includes people whose tumours have molecular markers. But the committee noted that it would consider the uncertainty because no evidence had been provided for the clinical or cost effectiveness for the subgroups with molecular markers.

Chemotherapy options in clinical practice

3.4 The comparators listed in the final NICE scope were:

- FOLFOX (folinic acid, fluorouracil, oxaliplatin)
- FOLFIRI (folinic acid, fluorouracil, irinotecan)
- CAPOX (capecitabine, oxaliplatin)
- capecitabine monotherapy.

The clinical expert explained that in UK clinical practice, both FOLFIRI and FOLFOX are commonly used as first-line treatments, with the CAPOX regimen typically used at second line. They noted the choice of chemotherapy is influenced by a range of individual patient factors and most people would have both oxaliplatin- and irinotecan-based regimens over the course of treatment. The clinical expert emphasised a preference for flexibility in clinical practice and, if recommended, bevacizumab should be able to be used with either oxaliplatin- or irinotecan-based regimens at first and second line. The NHS England clinical lead (from here, NHSE lead) and patient expert supported the need for flexibility in how bevacizumab is used with different chemotherapy regimens. The clinical expert stated that frailer, older people may be more likely to have bevacizumab with a single-agent fluoropyrimidine (such as capecitabine monotherapy) rather than

combination regimens because of toxicity.

The EAG did not identify any NICE technology appraisals or clinical studies evaluating bevacizumab plus capecitabine compared with capecitabine alone for first- or second-line treatment of mCRC. Previous NICE appraisals were informed by the regulatory trials informing the license for bevacizumab with fluoropyrimidine-based chemotherapy, in which the chemotherapies were FOLFIRI, CAPOX and FOLFOX. So, the EAG could not consider capecitabine monotherapy as a comparator in its assessment. A clinical expert explained that a common strategy in clinical practice is maintenance therapy. This typically involves using first-line treatments such as oxaliplatin for 4 to 6 months, then switching to a maintenance drug such as oral capecitabine to reduce toxicity and improve progression-free survival. The clinical expert noted that combining bevacizumab with oral capecitabine is common outside the UK and is increasingly used in colorectal cancer care because there is a clinical benefit of this strategy. The regulatory trials had not assessed using bevacizumab in addition to maintenance capecitabine. The committee concluded that the chemotherapy regimens outlined in the scope were used in clinical practice, and that it would consider the available evidence for all comparators in the first- and second-line setting. The committee acknowledged that capecitabine monotherapy may be more likely to be used by older and frailer people. But no evidence was available for bevacizumab plus capecitabine compared with capecitabine alone in the summary of product characteristics, so the committee could not determine its clinical and cost effectiveness. It considered the equality implications of this (see section 3.17).

Clinical effectiveness

First-line clinical effectiveness

3.5 The EAG's main evidence on the clinical effectiveness of bevacizumab plus fluoropyrimidine-based chemotherapy came from different sources. The EAG identified 2 clinical studies related to the first-line treatment of mCRC with bevacizumab plus fluoropyrimidine-based chemotherapy. These were:

- Study NO16966 (the primary source of clinical-effectiveness data for bevacizumab plus FOLFOX or CAPOX, and FOLFOX or CAPOX alone in TA212)
- Study AVF2107g (the primary source of clinical-effectiveness data for bevacizumab plus FOLFIRI, and FOLFIRI alone in TA118).

Study NO16966 was a phase 3, multicentre, multinational, randomised, open-label study. Data was from a 2-by-2 factorial part of the trial assessing the superiority of bevacizumab plus chemotherapy compared with placebo plus chemotherapy. The chemotherapy regimen was either FOLFOX-4 (that is, the FOLFOX regimen given every 2 weeks, with 2 long infusions in the first 48 hours) or CAPOX. In TA212, the committee concluded it was appropriate to assume CAPOX and FOLFOX were clinically equivalent and that data from the CAPOX and FOLFOX arms could be combined, as could data from the bevacizumab plus CAPOX and bevacizumab plus FOLFOX arms. Results from the 2-by-2 part of the trial (secondary pooled analysis) showed that bevacizumab plus chemotherapy (bevacizumab plus CAPOX and bevacizumab plus FOLFOX-4 combined) significantly improved progression-free survival compared with chemotherapy alone (placebo plus CAPOX and placebo plus FOLFOX-4 combined). For the intention-to-treat population, median progression-free survival was 9.4 months in the bevacizumab plus chemotherapy group, and 8.0 months in the chemotherapy group (a difference of 1.4 months). The

hazard ratio for remaining free of disease progression was 0.83, and median follow up was 28 months. Bevacizumab plus chemotherapy also improved overall survival compared with chemotherapy alone. For the intention-to-treat population, median overall survival was 21.3 months in the bevacizumab plus chemotherapy group, and 19.9 months in the chemotherapy group (a difference of 1.4 months). The hazard ratio for death was 0.89 at a median follow up of 28 months. Excluding data from people in the trial who had prior adjuvant therapy (the committee's preference in TA212, which was used in the EAG's model for the current evaluation) decreased the hazard ratio for progression-free survival and overall survival.

Study AVF2107g was a multicentre, international, phase 3 randomised controlled trial comparing first-line bevacizumab plus FOLFIRI compared with placebo plus FOLFIRI. Bevacizumab plus FOLFIRI improved progression-free survival compared with placebo plus FOLFIRI. Median progression-free survival was 10.6 months in the bevacizumab plus FOLFIRI group, and 6.2 months in the placebo plus FOLFIRI group (a difference of 4.4 months). The hazard ratio for remaining free of disease progression was 0.54. Median overall survival was 20.3 months for bevacizumab plus FOLFIRI and 15.6 months for placebo plus FOLFIRI (improving median overall survival by 4.7 months). The hazard ratio for death was 0.66. The committee concluded that bevacizumab plus FOLFOX, CAPOX or FOLFIRI offered better overall and progression-free survival than chemotherapy alone.

Second-line clinical effectiveness

3.6 The EAG identified Study E3200, which was the only clinical evidence informing the effectiveness of bevacizumab plus FOLFOX and FOLFOX alone for second-line treatment of mCRC in TA212. It also identified a meta-analysis by Mocellin et al. (2017). The EAG did not identify any previous NICE technology appraisals or relevant clinical studies for the

UK population evaluating bevacizumab plus FOLFIRI compared with FOLFIRI alone for the second-line treatment of mCRC.

Study E3200 was a phase 3, multicentre, 3-arm, randomised, open-label study. It compared bevacizumab plus FOLFOX-4, FOLFOX-4 alone, and bevacizumab alone in adults with advanced or mCRC that had been treated with a fluoropyrimidine and irinotecan, either separately or in combination. The bevacizumab-alone arm was stopped early because of poor efficacy. The primary endpoint was overall survival, with additional determinations of progression-free survival, response, and toxicity. Median progression-free survival was 7.3 months in the bevacizumab plus FOLFOX group, and 4.7 months in the FOLFOX alone group (a difference of 2.6 months). The hazard ratio for remaining free of disease progression was 0.61. Median overall survival was 12.9 months in the bevacizumab plus FOLFOX group, and 10.8 months in the FOLFOX alone group (a difference of 2.1 months). The hazard ratio for death was 0.75. The committee noted that the studies included in the Mocellin et al. (2017) meta-analysis, which included studies differing in fluoropyrimidine chemotherapy regimens, study location and bevacizumab dose, gave similar hazard ratios for progression-free survival and overall survival to those from Study E3200. People in Study E3200 had not previously had bevacizumab, which the EAG noted was a limitation, because the model for second-line treatment did not consider previous treatments (see section 3.9). But the EAG noted that data reported by Masi et al. (2015), a trial included in the Mocellin meta-analysis, indicated that previous bevacizumab use may not influence the efficacy of second-line bevacizumab. The committee concluded that bevacizumab plus FOLFOX offered better overall and progression-free survival than FOLFOX alone.

Methods for reviewing cost-effectiveness evidence

3.7 Given the expedited approach of this appraisal (see section 3.1), the EAG used a pragmatic approach for reviewing the cost-effectiveness evidence. So a systematic literature search was not done, and the manufacturers

did not submit economic models. Instead, the EAG reviewed previous NICE technology appraisals on bevacizumab plus fluoropyrimidine-based chemotherapy as first- and second-line treatments for mCRC. The EAG identified 2 NICE technology appraisals for first-line treatment (see TA118 and TA212) and 1 NICE technology appraisal for second-line treatment (see TA242). The committee considered this approach and concluded that, for the purposes of this pragmatic appraisal, the EAG's approach was appropriate.

Economic model

3.8 The EAG used a partitioned survival model approach to estimate the cost effectiveness of bevacizumab plus fluoropyrimidine-based chemotherapy (FOLFOX, FOLFIRI, CAPOX) compared with fluoropyrimidine-based chemotherapy alone, for the first- and second-line treatment of mCRC. Given the lack of identified evidence on the clinical efficacy of bevacizumab plus capecitabine (see section 3.4), this combination was excluded from the analysis. The economic analysis included 3 pairwise comparisons:

- Model 1: bevacizumab plus FOLFOX compared with FOLOX alone
- Model 2: bevacizumab plus FOLFIRI compared with FOLFIRI alone
- Model 3: bevacizumab plus CAPOX compared with CAPOX alone.

The models included 3 mutually exclusive and exhaustive health states: progression free, post-progression and dead. All people entered the model in the progression-free state and had treatment with either bevacizumab plus chemotherapy, or chemotherapy alone. For simplicity, the model assumed people only had best supportive care after disease progression, which was highlighted as a limitation by the EAG (see section 3.9). People in the model were redistributed across the 3 health states at the end of each monthly cycle. The committee considered the structure of the EAG's partitioned survival model. It acknowledged that the model used a standard approach to estimate

the cost effectiveness of cancer medicines and decided it was appropriate for decision making.

Key principles

Model includes one line of treatment

3.9 Given the expedited nature of this evaluation, and because the model was informed by historical trial data, the EAG did not run full sequential treatment models including interventions used later in the mCRC treatment pathway. The EAG highlighted that, given that the available data was from a time before current follow-on treatments were available, developing full sequential models across all treatment lines was not feasible. Instead, the model assumed that after disease progression, people would have best supportive care. As a result, costs and quality-adjusted life years (QALYs) associated with subsequent treatments were not included. The EAG thought that this approach was satisfactory in the context of this evaluation because:

- Subsequent treatments recommended by NICE after the relevant treatment line are cost effective. So extending life with first-line bevacizumab plus chemotherapy would increase the overall net monetary benefit of a treatment strategy. If subsequent treatments are cost effective, then for each pound spent, they would generate health benefits that meet the threshold needed for cost effectiveness.
- It was reasonable to assume that the relative effectiveness of subsequent treatments would not be affected by earlier use of bevacizumab.

The EAG noted that this approach was likely to underestimate life expectancy and QALYs associated with the standard care arm, which was important when considering whether the severity modifier was applicable (see section 3.16). The committee agreed that, given the data and time limitations, the approach was reasonable for this type of

review. It further agreed that it was reasonable to assume that the relative effectiveness of later treatments and their cost effectiveness would not be affected by earlier bevacizumab because:

- The hazard ratios reported by Masi et al. (2015) (for bevacizumab used at second line after first-line bevacizumab) were similar to those from studies in which bevacizumab was not used at first line. A clinical expert noted that they expected maintained efficacy of bevacizumab on repeated use, and that if efficacy decreased, the decrease would be expected to be small.
- The clinical experts stated that the clinical trials used to inform the clinical-effectiveness estimates of subsequent treatments (in the NICE appraisals of those medicines) were international and had included people who had previously had bevacizumab. So the impact of having previous bevacizumab may have been captured to some extent.

The committee acknowledged that the EAG did not model full treatment sequences beyond the relevant line of therapy. The committee would have preferred subsequent treatments to be modelled, but it agreed that the EAG's approach was appropriate in the context of this pilot. It noted that it would take the uncertainty resulting from this approach into account in its decision making.

Survival extrapolations

3.10 Studies NO169665 and AVF2107g were the primary sources of first-line clinical-effectiveness evidence for bevacizumab plus FOLFOX or CAPOX compared with FOLFOX or CAPOX alone, and bevacizumab plus FOLFIRI compared with FOLFIRI alone, respectively (see section 3.5). E3200 was the primary source of second-line clinical-effectiveness evidence for bevacizumab plus FOLFOX compared with FOLFOX alone (see section 3.6) The EAG did not have access to individual patient-level data from these studies, so it generated pseudo-individual patient data for progression-free survival and overall survival. The EAG independently

fitted standard parametric survival models to the pseudo-individual patient data to extrapolate beyond the period for which there was trial data. To select the most appropriate parametric distributions to model progression-free survival and overall survival, the EAG assessed:

- the statistical fit to the Kaplan–Meier data using the Akaike information criterion and Bayesian information criterion
- the visual fit of fitted survival curves against the trial data
- the clinical plausibility of the survival model predictions (based on hazard plots and input from clinical experts). Clinical expert advice to the EAG was that the hazards should be consistently increasing for both progression-free survival and overall survival. So, the EAG prioritised models with consistently increasing hazard trends in its base case and explored alternative models in scenario analyses.

The same distributions were applied across treatment arms. The EAG also preferred to use the same distribution for both progression-free survival and overall survival within each pairwise comparison. The EAG selected scenarios of alternative parametric distributions that were plausible and provided the widest possible range of plausible incremental cost-effectiveness ratios (ICERs). These were:

- for first-line treatment:
  - the gamma distribution for progression-free survival and overall survival in models 1 and 3 (with the log-logistic used in scenario analyses)
  - the Weibull distribution for progression-free and overall survival in model 2 (with generalised gamma in scenario analyses)
- for second-line treatment: the gamma distribution for progression-free survival and overall survival in models 1 and 3 (with the log-logistic used in scenario analyses).

The choice of distribution had a moderate impact on the ICER. The

committee noted that, in principle, it would prefer the distributions for progression-free survival and overall survival not to be restricted to using the same distribution. But after reviewing the distributions used, it noted that using different distributions for progression-free survival and overall survival made very little difference to the results. The committee concluded it agreed with the EAG's base-case parametric distributions for extrapolating progression-free survival and overall survival.

Bevacizumab weighted mean price

3.11 A range of confidential prices for bevacizumab originator and biosimilars is listed in the Medicines Procurement and Supply Chain (MPSC; see section 4.4.4 in NICE's health technology evaluations manual). NICE originally advised the EAG to use the unweighted mean MPSC price of bevacizumab, and the EAG was not provided with data on market share for the originator and for each biosimilar. The EAG's report noted that because of the range of prices for products in the MPSC, it would prefer to use a weighted mean based on market share to reflect usage in the NHS. After further consideration, NICE asked the EAG to use the mean MPSC price weighted by market share (based on bevacizumab usage across all indications) in its analyses. For this pilot approach, NICE asked the committee to use the weighted mean price in its decision making. The committee noted that regional variation in procurement practices may lead to differences in access to bevacizumab biosimilars across the NHS, and the cheapest product may not always be selected. The committee noted that although mean biosimilar prices would be expected to remain stable or reduce over time, this was uncertain. The prices of bevacizumab products in the MPSC are confidential so the weighted and unweighted mean prices cannot be reported here. The committee concluded that it would use the weighted mean price of bevacizumab products in the MPSC as indicative of the cost of bevacizumab, and take into account the uncertainty about this estimate in its decision making.

Vial sharing

3.12 The NHSE lead asked whether the EAG had incorporated vial sharing in its analyses. They noted that colorectal cancer is common, and bevacizumab is also used in other tumour types (such as hepatocellular carcinoma and gynaecological cancers). So if bevacizumab were recommended, there would be significant opportunity for vial sharing across the NHS. The clinical expert agreed and highlighted that vial sharing is standard practice in many cancers and is done routinely by hospital pharmacies. The EAG explained that vial sharing was explored in a scenario analysis, which showed a minimal reduction in the ICER, but it was not included in its base case. The committee acknowledged that vial sharing is standard practice and is likely to be feasible for bevacizumab. It acknowledged that the EAG had explored vial sharing in a scenario analysis and concluded the impact was minimal.

Utility values

Source of utility values

3.13 The EAG considered utility values reported from previous NICE technology appraisals for first-line treatment (TA118 and TA212) and second-line treatment (TA1008) to select its preferred estimates for this evaluation. It also included disutilities related to adverse events, which had not been considered in these appraisals (see section 3.14). For the first-line setting, the EAG followed the external review group (ERG)'s model assumptions from TA212 by assuming a utility value of 0.77 for the progression-free health state and 0.68 for the progressed-disease health state in its base case. For the second-line setting, the EAG followed the committee's preferences from TA1008 by assuming a utility value of 0.73 for the progression-free health state and 0.64 for the progressed-disease health state in its base case. All health-state utility values were adjusted for ageing using Hernandez Alava et al. (2022) (see section 4.3.16 in NICE's health technology evaluations manual). The EAG explored uncertainty in the utility values in the first- and second-line settings by

arbitrarily increasing and decreasing them by 5% in scenario analyses.

The committee noted that the utility values in the previous appraisals were not based on data collected in the bevacizumab trials. It also noted that the utility values used in the second-line setting were similar to those used in the first-line setting. The clinical expert highlighted that people considered for second-line treatment are generally similar to those having first-line treatment and therefore considered it reasonable for the utility values to be comparable. The committee acknowledged that the utility values were sourced from previous technology appraisals. It would have preferred to use trial-based data but concluded that the EAG's approach was pragmatic given the limitations in the available evidence. The committee noted that the utility values chosen by the EAG for the first- and second-line settings were similar, but concluded this was reasonable.

Disutility for adverse events

3.14 The EAG applied adverse event-related disutilities in the model to estimate the reduction in health-related quality of life for the duration of the adverse events. In the first-line setting, adverse event frequencies for bevacizumab plus FOLFOX or CAPOX and FOLFOX or CAPOX alone were based on Study NO16966. Adverse event data for bevacizumab plus FOLFIRI and FOLFIRI alone came from Study AVF2107g. In the second-line setting, the frequencies of adverse events were taken from Study E3200. The EAG applied a one-off disutility for adverse events by multiplying the estimated disutility of each adverse event by its respective duration and frequency. It assumed that each adverse event lasted for 14 days, based on clinical opinion. The EAG did a targeted literature search for disutility values, and the values used in the model were taken from the literature, previous NICE technology appraisals and assumptions relating to proxy conditions. The QALY losses for all adverse events were added to estimate a one-off QALY loss which was applied in the first model cycle. The committee noted that the previous technology appraisals did not include disutilities for adverse events. The patient expert highlighted

that adverse events are a routine part of chemotherapy and are managed through a joint approach between the healthcare professionals and the patient. They explained that management is about balancing factors such as dose adjustments and treatment breaks. They emphasised that adverse events should be taken into consideration, noting that bevacizumab has its own adverse event profile. The EAG highlighted that it explored increasing adverse event disutilities by 10 times in scenario analyses, which had a minimal impact on the ICER. The committee acknowledged the views of the patient and clinical experts. The committee concluded that adverse event disutilities should be included in the model.

Costs

Drug administration and monitoring costs

3.15 Unit costs and resource use for each treatment were based on regimens from Study NO16966 (first- and second-line) and Study AVF2107g (first-line). The EAG highlighted that current practice uses modified de Gramont regimens (for FOLFIRI-containing regimens only) and stops oxaliplatin after 6 months because of toxicity (FOLFOX and CAPOX regimens). These adaptations were explored in sensitivity analyses, assuming the same efficacy as in the base case. The EAG noted the results from these may better represent current clinical practice. Results from the scenario analyses showed that stopping oxaliplatin at 6 months had minimal impact on the ICERs for bevacizumab plus FOLFOX or CAPOX, and using a modified de Gramont regimen for FOLFIRI-containing regimens had a moderate impact. The committee acknowledged that the trial regimens informing the economic model were based on older protocols that differ from those currently used in NHS practice. It noted that the second-line trial used a double dose of bevacizumab, and using the FOLFIRI regimen (used in the NHS) reduced costs. It concluded that it was appropriate to use dosing regimens used in the NHS to estimate costs rather than those used in the trials.

Severity modifier

3.16 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The EAG noted that its modelling approach (including 1 line of treatment) underestimated the life expectancy and QALYs associated with standard care. To address this, the EAG attempted to estimate QALYs gained from later lines of treatment and add them to those accrued in the evaluated treatment line. The EAG noted that this approach was likely to overestimate the QALYs of current care. This is because it may have double counted the QALYs accrued between disease progression and death, and may not have accounted for people who die before having subsequent treatment, which was a methodological limitation. The EAG noted that this could be unfavourable to bevacizumab, if the proportional or absolute QALY shortfall calculated from this estimate fell just below the threshold needed for applying a higher QALY weight.

In the first-line setting, the expected total QALYs were estimated as the sum of total QALYs from the comparator group in the first- and the second-line models and the reported QALYs for trifluridine–tipiracil plus bevacizumab reported in TA1008. In the second-line setting, the expected total QALYs were estimated as the sum of total QALYs from the comparator group in the second-line model and the trifluridine–tipiracil plus bevacizumab group in TA1008. The absolute and proportional QALY shortfalls were estimated using the University of York QALY shortfall calculator, assuming:

- people having first-line treatment had a mean age of 60 years, with 40% of the cohort being female
- people having second-line treatment had a mean age of 61 years, with 39.5% of the cohort being female.

The results of the QALY shortfall analysis estimated that in second-line treatment a disease severity modifier of 1.2 would apply, but that for first-line treatment no modifier would be appropriate. The committee noted substantial limitations in the EAG's approach to estimating the QALY shortfall, which the EAG had acknowledged. But the committee thought that the approach likely overestimated QALYs in the standard care arm, increasing the committee's confidence that a 1.2 weighting in the second-line setting was appropriate. The committee noted that using a modifier of 1.2 was not inconsistent with severity modifiers applied in recent later-line appraisals. It acknowledged the potential limitations of the non-sequential modelling approach in estimating QALY shortfall. But it concluded that it had been presented with a worst-case scenario, so a severity modifier of 1.2 for second-line treatment was appropriate.

Equality

3.17 The committee noted that were no potential equality issues identified during the scoping process. The clinical and patient experts did not think there were any equality issues that had not been addressed in this evaluation. The committee noted that capecitabine monotherapy may be more likely to be used by older and frailer people who cannot tolerate combination chemotherapy. But without evidence of a clinical benefit from adding bevacizumab to capecitabine for people who would otherwise have capecitabine alone, it was not possible to make a specific recommendation for this group. Although there may be a higher proportion of older people in this group there was no evidence presented that chemotherapy treatment options would be determined on the basis of age alone. So, the committee was satisfied its recommendations do not discriminate on the basis of age. Also, its recommendations do not state a preference for any particular chemotherapy regimen in first- or second-line treatment. This allows flexibility for deciding which chemotherapy bevacizumab is added on to out of the chemotherapy options that had

informed the marketing authorisation for bevacizumab, that is FOLFOX, CAPOX or FOLFIRI.

Cost-effectiveness estimates

Acceptable ICER

3.18 NICE's health technology evaluations manual notes that above a most plausible 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 will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee acknowledged that there is an unmet need for people with mCRC. The committee noted the uncertainties in the costs of bevacizumab and the economic model assumptions, and those that came with the EAG's pragmatic approach. Because of these uncertainties, the committee concluded that an acceptable ICER would be towards the lower end of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained).

EAG cost-effectiveness estimates

3.19 The exact cost-effectiveness estimates cannot be reported here because of confidential discounts for bevacizumab. For the first-line setting, the EAG's base-case ICERs were within the range that NICE considers an acceptable use of NHS resources for the models in which bevacizumab was an add on to FOLFOX, FOLFIRI or CAPOX. For the second-line setting, with a 1.2 weighting applied for severity, the EAG's base-case ICERs were also within the range that NICE considers an acceptable use of NHS resources, for the models in which bevacizumab was an add on to FOLFOX or CAPOX. The committee accepted the EAG's base-case assumptions. But it noted that scenarios reflecting the dosing regimen of

chemotherapy used in the NHS should be included in the base case. In the absence of a specific model for bevacizumab plus FOLFIRI in the second-line setting, the committee thought it appropriate to use the ICERs from the FOLFOX and CAPOX models to indicate the cost effectiveness of bevacizumab with chemotherapy, regardless of the chemotherapy regimen. The committee concluded that it could not determine the cost effectiveness of capecitabine monotherapy, because no evidence was provided.

Conclusion

Recommendation

3.20 The committee concluded that bevacizumab plus fluoropyrimidine-based chemotherapy improves progression-free and overall survival in mCRC compared with fluoropyrimidine-based chemotherapy alone. The most likely cost-effectiveness estimates for bevacizumab plus fluoropyrimidine-based chemotherapy are below what NICE considers a cost-effective use of NHS resources. So, bevacizumab (originator and biosimilars) plus fluoropyrimidine-based chemotherapy can be used in the NHS.

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 90 days 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 60 days 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 bevacizumab (originator or biosimilars) with fluoropyrimidine-based chemotherapy 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 technologies 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, a project manager and an associate director.

Janet Boadu

Technical lead

Mary Hughes

Technical adviser

Jeremy Powell

Project manager

Emily Crowe

Associate director

ISBN: [to be added at publication]

Issue date: November 2025