National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG124 Bevacizumab | Advice Document v1.0| July 2025

Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the second-line treatment of adult patients with metastatic carcinoma of the colon or rectum.[A]

NCMAG Decision | this off-patent use of bevacizumab biosimilars is supported

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith Scottish Medicines Consortium remit. For more detail on NCMAG remit please see our website.

Decision Rationale

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness of bevacizumab in the proposed population. After consideration of all relevant information under the Decision-making Framework for Value Judgements, the Council made a decision to support this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland oncologists treating colorectal cancer
Medicine Name	Bevacizumab
Cancer type	Gastrointestinal Cancer
Proposed on-label and off-patent use	Second-line treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy[1]

Medicine Details	Form: intravenous infusion Dose: 5mg/kg every 14 days or 7.5mg/kg every 21 days, depending on chemotherapy regimen used in combination It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.
Advice eligibility criteria	Inclusion criteria: • One previous line of treatment for metastatic disease. • No prior bevacizumab for metastatic disease • 18 years of age or older

1. Current Management Context

Colorectal cancer, incidence and prognosis

Metastatic colorectal cancer occurs when the cancer has spread to a distant organ or lymph node[2]. The most common sites for metastases are the liver, lungs, peritoneum and distant lymph nodes[3]. Patients typically present with symptoms such as rectal bleeding, change in bowel habit, and abdominal pain[4].

In Scotland, there were 829 patients diagnosed with metastatic colorectal cancer at time of first diagnosis in 2022. Additionally, 1829 patients were diagnosed with stages II and III colorectal cancers. ESMO estimates that 20-50% of these (366-915 patients) will relapse, giving an estimated range of patients with newly diagnosed metastatic disease in Scotland between 1195 and 1744 patients annually[3, 4]. This corresponds to an incidence of fewer than 5 per 10,000 diagnosed with metastatic disease per year and meets orphan-equivalent criteria. Fewer than 20% of patients with metastatic disease will survive beyond five years[4]. The mean age of diagnosis with bowel cancer is 71 years of age[5].

Metastatic colorectal cancer treatment pathway in NHSScotland

First line chemotherapy varies depending upon the genetic profile of the cancer, including the mutation status of the RAS gene, BRAF gene and if microsatellite instability-high (MSI-H) and the site of origin of the cancer. In metastatic colorectal cancer a RAS gene mutation is estimated to be present in approximately 40% of patients[6], BRAF mutation in 10% and MSI-H in 5%. If the primary tumour and metastases are resectable these can also be removed with curative intent. Some patients may require downstaging chemotherapy to reduce cancer burden and support surgical removal[7].

The options for second line treatment are influenced by prior treatment received as well as patient specific factors, genetic profile of cancer, performance status and comorbidities. For example, patients that have received oxaliplatin based therapy as first line treatment would generally receive irinotecan with fluoropyrimidine in the second line or vice versa[3, 7].

In current practice, patients would be eligible to receive a range of different second line treatments including: capecitabine monotherapy; fluorouracil plus folinic acid; fluorouracil, folinic acid and oxaliplatin (FOLFOX); capecitabine and oxaliplatin (CAPOX/XELOX); fluorouracil, folinic acid and irinotecan (FOLFIRI); and aflibercept, fluorouracil, folinic acid and irinotecan (AFLIB plus FOLFIRI). Both irinotecan and oxaliplatin-based regimens are considered equally effective, so treatment selection and sequencing are guided by individual patient factors or the regimen toxicity profiles[8, 9].

In metastatic colorectal cancer that is MSI-H or mismatch repair (MMR) deficient, patients will generally receive immunotherapy in the first line and chemotherapy in the second line setting.

Encorafenib in combination with cetuximab is offered to patients that have BRAF mutant disease and that have received prior systemic therapy[7].

AFLIB plus FOLFIRI is routinely accessible in the second line setting after previous treatment with oxaliplatin; aflibercept is a similar class of medicine as bevacizumab.

Bevacizumab is licensed for use in combination with fluoropyrimidine-based chemotherapy for the treatment of metastatic colorectal cancer, therefore, bevacizumab could be used in combination with any regimens that contain capecitabine or fluorouracil. However, when it was on patent it was not recommended following health technology assessment review, so is not routinely accessible in NHSScotland for this use[10, 11].

International Context for proposed use

The European Society for Medical Oncology (ESMO), The American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) support the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for the second-line treatment of patients with colorectal cancer [3, 12, 13]. As a standard of care internationally, clinical trials often require patients to have received prior bevacizumab or for a bevacizumab regimen to be routinely accessible to the study control arm participants: this currently limits clinical trial opportunities in NHSScotland.

Pharmacology of bevacizumab

Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), inhibiting the binding of VEGF to its receptors, on endothelial cells. This inhibits the formation of new tumour vasculature and reduces tumour growth[1].

2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were bevacizumab, colorectal cancer. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key studies were critically appraised using the Cochrane risk of bias version 2.0 tool and non-randomised studies were appraised using the risk of bias in nonrandomised studies tool[14, 15].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The E3200 study was identified as supporting the use of bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) in adults with previously treated metastatic colorectal cancer. The E3200 study was a phase III, randomised, open-label study conducted in the US and South Africa. The study contained three treatment arms: FOLFOX4 plus bevacizumab, FOLFOX4 only, and bevacizumab monotherapy. The study included patients with histologically confirmed colorectal cancer, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, that had previous chemotherapy with irinotecan and a fluoropyrimidine, and a maximum blood pressure of 150/100 mmHg on antihypertensives[1]. Patients were excluded if they had previously received bevacizumab or oxaliplatin, had a thrombotic or haemorrhagic event in the prior 6 months, or required therapeutic anticoagulation[16].

Patients were randomised on a 1:1:1 ratio to receive FOLFOX4 plus bevacizumab (n=286), FOLFOX4 alone (n=291), or bevacizumab monotherapy (n=243). Bevacizumab monotherapy is not relevant for this proposal and this arm will not be described further. Randomisation was stratified by prior radiation therapy and Eastern Cooperative Group (ECOG) performance status (PS)[16].

The primary outcome was overall survival defined as the time from randomisation to death from any cause. Secondary outcomes included progression free survival which was defined as the time from random assignment to progression or death, if it was within four months of the last assessment. The response assessments were reported by the investigators and not independently reviewed. Safety was also evaluated[16].

Results

The median age was 62 years (range 21-85 years) in the FOLFOX 4 plus bevacizumab arm and 61 years (range 25-84 years) in the FOLFOX4 arm. Almost all patients (approximately 95% in both arms) had baseline ECOG performance scores of 0 to 1 and 40% of participants were female[16].

The study met its primary and secondary outcomes, showing statistically significant improvement in overall survival and PFS when bevacizumab was added to FOLFOX4. Detailed results are presented in Table 1[16].

Table 11| Results from the E3200 study for primary and secondary outcomes using the intention to treat population[16]

	FOLFOX4 plus bevacizumab (n=286)	FOLFOX4 alone (n=291)
Median follow up, months	28	
Primary outcome - overall survival		

Median survival, months	12.9	10.8
Hazard ratio for death	0.75	
p-value	p = 0.0011	
Progression free survival		
Median progression-free survival, months	7.3	4.7
Hazard ratio for PFS	0.61	
p-value	p < 0.001	
One year survival, %	56	43
p-value	p < 0.001	
Response		
Overall response	22.7%	8.6%
Complete response	1.7%	0.7%
Partial response	21%	7.9%

Abbreviation: FOLFOX4 - oxaliplatin, fluorouracil, and leucovorin; PFS – progression free survival

Patient reported outcomes

There were no patient reported outcomes documented in this study.

Safety evidence

This is an on-label use which has been considered by a regulator to have an acceptable safety profile. Patients assigned to receive FOLFOX4 plus bevacizumab had a median duration of therapy of 10 cycles, compared with seven cycles for FOLFOX4 alone and four cycles for those assigned to bevacizumab alone[16].

Selected grade 3 or 4 adverse events (AE) were reported with a higher incidence in the FOLFOX4 plus bevacizumab treatment arm compared with FOLFOX4 alone (75% versus 61%)[16]. These included higher rates of neuropathy, hypertension, thromboembolism, vomiting and bleeding when compared with those who received FOLFOX4 alone[16]. The majority of bleeding events with FOLFOX4 plus bevacizumab occurred in the GI tract[16].

There were three reports of bowel perforation in the FOLFOX4 plus bevacizumab arm. There was one death attributable to bowel perforation in the FOLFOX4 plus bevacizumab treatment arm[16].

There were no significant differences in the incidence of adverse events leading to treatment discontinuation or in 60-day all-cause mortality[16].

Supportive studies

Two supportive studies were identified, one single arm trial as well as a systematic review[17].

BEVACOLOR study

The BEVACOLOR study was a phase II, single arm, multicentre study. It included adults with an ECOG PS of 0 to 2 and histologically confirmed metastatic colon or rectal cancer that had progressed or relapsed after first line treatment with one oxaliplatin- or irinotecan-based regimen[17]. Patients received investigators choice of second line chemotherapy plus bevacizumab: dosing depended on the choice of chemotherapy regimen and was given as 5mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks. Treatment continued until disease progression[17]. The primary endpoint was disease control rate (DCR) defined as the proportion of patients in the intent-to-treat (ITT) population that achieved a best response (according to RECIST) of complete response (CR), partial response (PR), or stable disease during the study treatment period [17].

Results

Fifty-three patients were included in the intention to treat and safety populations. Sixty-six percent were male, and median age was 62 years. Previous first line regimens were FOLFOX (53%), FOLFIRI (22%), CAPOX (also known as XELOX) (20%) or other (5%). Second line treatments given in combination with bevacizumab were FOLFIRI (57%), FOLFOX (26%), irinotecan (15%) and CAPIRI (otherwise known as XELIRI) (2%). The median duration of chemotherapy plus bevacizumab treatment was 5.6 months (range, 0.9 to 13.2 months)[17].

Table 2 Results for the primary and secondary outcomes of BEVACOLOR[17]

	Chemotherapy plus bevacizumab (n=53)	Irinotecan-based chemotherapy (n=39)	Oxaliplatin-based chemotherapy (n=14)
Primary outcome			
Disease control rate	87%	90%	79%
Complete response	2%	3%	0%
Secondary outcomes			
Median follow-up, months	16.4		
Median overall survival, months[a]	19.3	22.4	13.9
Median progression-free survival, months[b]	6.5	7.8	5.3

[A] number of overall survival events not reported

[B] 98% of study patients had a progression-free survival event at the time of reporting

Beretta meta-analysis

The systematic review and meta-analysis, referred to as the 'Beretta meta-analysis' from this point on, included eleven studies examining FOLFIRI and bevacizumab in the second line in patients with metastatic colorectal cancer previously treated with oxaliplatin[18]. The systematic review included a mixture of study designs; one phase II RCT, two phase II single arm studies, one cohort study and

seven retrospective studies resulting in 435 included patients. A pooled analysis resulted in an overall response rate of 26% (range 22.5 to 30.8 %). Heterogeneity was judged to be low therefore fixed effects were used in the analysis. Median disease control rate was 82.9% (range 60.3 to 92.3%). Mean PFS was 8.6 months and the mean OS, was 18.4 months.

Quality assessment of clinical evidence

Study E3200[16] was judged to have a low risk of bias though some concerns were identified using the Cochrane Risk of Bias version 2 tool[14]. It is not clear how randomisation was processed; electronic methods and central randomisation can reduce the risk of bias. The study used an open-label design meaning patients and clinicians were not masked to treatment allocations. Regarding measurement of study outcomes, response assessments were reported by investigators and were not independently reviewed allowing the potential for bias on the assessment of response.

The BEVACOLOR study was assessed for bias using Cochrane's risk of bias in nonrandomised studies tool[15, 17]. Three domains; baseline confounding, measurement of the outcome and bias selection of the reported result, were at a serious risk of bias which meant that the overall assessment was deemed to be at a critical risk of bias. Therefore, the results of the BEVACOLOR study should be interpreted with caution.

Clinical effectiveness considerations

The addition of bevacizumab to FOLFOX4 as a second-line treatment of metastatic colorectal cancer has been shown to improve overall survival and progression-free survival

The addition of bevacizumab to FOLFOX4 resulted in a statistically significant improvement in median overall survival, 12.9 months compared with 10.8 months. Furthermore, median PFS was also significantly improved with the addition of bevacizumab to FOLFOX4, 7.3 months compared with 4.7 months[16]. Approximately 45% of patients are expected to have bevacizumab added to an oxaliplatin based regimen in the second line setting. Subsequent treatments were not reported, and their impact on overall survival is unknown.

Bevacizumab may have efficacy when added to irinotecan-based regimens.

In the treatment of metastatic colorectal cancer the sequencing of oxaliplatin or irinotecan containing regimens as first or second line therapy is not expected to affect outcomes, as long as patients receive all available drugs at some point[8, 9]. The choice is based on patient specific factors including genetic profile of cancer, performance status, comorbidities and prior treatments. There is some uncertainty on the efficacy of bevacizumab when used with chemotherapy regimens other than FOLFOX4 in the second line setting. The single-arm BEVACOLOR study and the Beretta systematic review may offer some reassurance, though the evidence is non-comparative. Bevacizumab has been used in combination with irinotecan as a standard of care in both first-line and second-line settings across multiple clinical trials[19-21]. NHSScotland clinical experts estimate irinotecan-based regimens are used in approximately 35% of the proposed patient population.

There is some uncertainty on the comparative efficacy and safety of bevacizumab plus chemotherapy compared to AFLIB plus FOLFIRI

Aflibercept, a VEGF inhibitor, combined with FOLFIRI is routinely accessible for second-line treatment in patients who have progressed on or are resistant to an oxaliplatin containing regimen, and NHSScotland clinical experts estimate it is currently used in approximately 15% of the proposed patient population[22]. In the VELOUR study, the addition of aflibercept to FOLFIRI was associated with a statistically significant increase in median OS from 12 to 13.5 months[23]. However, no head-to-head randomised trials have compared bevacizumab with aflibercept in the second-line setting. A network meta-analysis comparing bevacizumab plus chemotherapy with AFLIB plus FOLFIRI in second line RAS wild type patients reported no evidence of a difference for both OS and PFS. Central estimates indicated a trend favouring the bevacizumab regimen[24]. No direct evidence was identified comparing the safety and tolerability of aflibercept to bevacizumab, however, naive across-trial comparisons and retrospective data suggest that bevacizumab may be better tolerated[25, 26].

The proposed dosing of bevacizumab is lower than that used in the E3200 study.

The proposed bevacizumab dosing of 5 mg/kg every 14 days or 7.5 mg/kg every 21 days is licensed but is lower than the dosing used in the E3200 study. The E3200 study was conducted before a dose-finding study in the first-line setting suggested that an equivalent dose of 2.5mg/kg per week of bevacizumab was as effective as 5 mg/kg per week, with fewer side effects[27]. This lower dose has since become standard practice[27].

The EAGLE study compared bevacizumab 2.5 mg/kg and 5 mg/kg per week doses in combination with FOLFIRI after first-line bevacizumab and found similar efficacy[28]. Evidence from both the Beretta systematic review and BEVACOLOR study may also support the efficacy of the lower dose.

There may be generalisability concerns with the evidence

A NHSScotland real world data report examined first-line metastatic colorectal cancer patients who received systemic anticancer therapy (SACT) between the 1st January 2018 to 31st December 2022. The median age of patients treated with any SACT regimen was 68 years; with 35% being PS 0, 56% PS 1 and 7% PS 2 or worse. The E3200[16] and BEVACOLOR[17] studies included younger patient populations, with better performance status and this may reduce the generalisability of the results to NHSScotland.

There are some uncertainties about the generalisability of the E3200 study findings in relation to the NHSScotland population. The study recruited patients in South Africa and the United States, where there are different population characteristics and health systems. The subsequent treatments used in NHSScotland today are not reflected in the study (conducted around 20 years ago). Finally, the FOLFOX4 regimen used in the study delivers a lower total dose of fluorouracil and has less convenient administration than the proposed mFOLFOX6 regimen[16].

The safety profile of on-label bevacizumab in combination with fluoropyrimidine chemotherapy is well-characterised.

Across the evidence, the rates and types of adverse effects were similar, with the addition of bevacizumab increasing the incidence of hypertension, proteinuria, bleeding, thrombotic events, perforations, fistula formation, and impaired wound healing. There were higher rates of peripheral neuropathy in the E3200 study which is likely due to longer duration of oxaliplatin administration. Naïve comparisons may suggest that aflibercept has higher rates of adverse events than bevacizumab, although there is limited direct evidence to support this[26].

4. Patient Group Summary

We received a statement from Bowel Cancer UK who are a registered charity. Bowel Cancer UK reported 3.5 to 4% of their annual funding came from the pharmaceutical industry in 2024. A representative from Bowel Cancer UK attended the NCMAG council meeting. The key points from the submission are:

A diagnosis of metastatic colorectal cancer profoundly affects patients, with a prognosis of less than 20% survival after five years. Treatment is difficult for patients to endure and the disease impacts patients' families and loved ones too.

Treatment for metastatic colorectal cancer requires hospital appointments, and current treatments have debilitating side effects. Depending on specific mutations, such as the KRAS mutation, patients may have fewer effective therapeutic options available to them.

Bevacizumab plus chemotherapy may cause more side effects for patients, but patients felt that this was a worthwhile trade-off because the improvements in overall survival would lead to more time with loved ones.

5. Benefit-Risk Balance

The addition of bevacizumab to fluoropyrimidine chemotherapy is on-label and the UK medicines regulator has judged the regimen to have a favourable benefit-harm balance[1]. Bevacizumab has been shown to improve overall survival and PFS in the second-line setting.

6. Council Review | Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were satisfied that the clinical case had been made for bevacizumab in combination with fluoropyrimidine-based chemotherapy for the second-line treatment of adult patients with metastatic carcinoma of the colon or rectum.

7. Economic Evidence Review Summary

Economic Overview

The literature search for economic evidence on this topic returned few cost-effectiveness publications which evaluated bevacizumab in second-line treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy in the proposed population. One of these was UK-based National Institute for Health and Clinical Excellence's (NICE) Technology Appraisal of on-patent bevacizumab (in combination with non-oxaliplatin chemotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy, published in 2012[29]. The primary evidence in the appraisal was derived from E3200 study where the focus was oxaliplatin-based chemotherapy[16]. Due to a lack of clinical evidence evaluating bevacizumab in combination with non-oxaliplatin based chemotherapy at the time of the appraisal, a cost-effectiveness analysis was not performed.

Type of economic evaluation

In the absence of a cost-effectiveness analysis, a de-novo cost-comparison analysis has been performed to support this assessment.

Population, intervention, comparator and outcomes

The population used in the study were adult patients with metastatic colorectal cancer with no prior bevacizumab. The intervention was bevacizumab 5mg/kg every 14 days or 7.5mg/kg every 21 days, depending on chemotherapy regimen used in combination. The comparator consisted of four chemotherapy regimens commonly used in clinical practice across Scotland. The distribution of patients across these regimens was informed by clinical expert opinion and used to calculate a weighted average cost of the comparator. Treatments used in fewer than five percent of the patients were excluded from the analysis; the remaining proportions were then rescaled to maintain their relative ratios. The excluded regimens were single agent capecitabine or irinotecan, encorafenib plus cetuximab, nivolumab plus ipilimumab and raltitrexed-based chemotherapy. Therefore, the comparator comprised of CAPOX (37%), FOLFOX (18%), FOLFIRI (24%) and AFLIB plus FOLFIRI (21%), henceforth, referred as NHSScotland SOC.

The chemotherapy regimens proposed in combination with bevacizumab are expected to follow the same distribution as observed in NHSScotland SOC, with the exception of AFLIB plus FOLFIRI regimen, which is not prescribed in combination with bevacizumab. Proportions were subsequently adjusted to account for this change. As a cost-comparison analysis has been performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

Costs included were medicine acquisition, administration and adverse event costs for one year of treatment. Confidential NHSScotland Patient Access Scheme (PAS) and National Framework prices for off-patent medicines were used (accessed April 2025). In addition, multiple brands of

bevacizumab biosimilars are available under an NHSScotland National Framework contract. Therefore, the medicine acquisition cost of bevacizumab was calculated using a weighted average cost of the two most frequently used biosimilars across NHS Boards in Scotland, based on proportion of overall use, available from NHSScotland procurement database (accessed April 2025).

Treatment duration for CAPOX with and without bevacizumab, FOLFOX with and without bevacizumab and FOLFIRI with bevacizumab were informed by the E3200 study, while FOLFIRI alone and AFLIB plus FOLFIRI treatment durations were informed by the VELOUR study. In the E3200 study, patients receiving FOLFOX-4 and bevacizumab had a median of 10 cycles, versus 7 cycles for FOLFOX-4 alone, while the VELOUR study reported median cycles of 9 and 8 in the AFLIB and placebo groups, respectively[16].

The administration cost for intravenous medicines was based on delivery of either simple or complex parenteral chemotherapy depending on nurse and chair time for delivery of the required number of cycles (NHS National Reference costs 2023-25). Based on clinical expert opinion, the medicine administration costs for all cycles of FOLFOX and FOLFIRI was assumed to involve administration of complex parenteral chemotherapy. The first cycle of bevacizumab was assumed to involve administration of complex parenteral chemotherapy, while the following cycles were assumed to involve administration of simpler parenteral chemotherapy.

The costs associated with inpatient hospitalisation and management of grades 3 or 4 vomiting and bleeding were calculated using adverse event rates from the E3200 study and NHS reference costs 23-25 for non-elective hospital stay less than five days.

Results

All figures in the cost-comparison exclude VAT.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Table 3: Summary of cost-comparison results (confidential price, excluding VAT)

Cost category	Medicine acquisition (£)	Medicine administration (£)	Adverse event (£)	Total costs per-patient (£)
Bevacizumab plus chemotherapy[a]	CIC	5,525	145	CIC
NHSScotland SOC[b]	CIC	3,095	31	CIC
Cost difference	CIC	2,429	114	CIC(cost increasing)

[a]Refers to chemotherapy (CAPOX, FOLFOX or FOLFIRI) which is assumed to be given for longer duration along with bevacizumab compared to NHSScotland SOC (chemotherapy alone), based on findings from E3200 and VELOUR studies.
[b]NHSScotland SOC refers to basket of four chemotherapy regimens described above.
Key: CIC = commercial-in-confidence; SOC = standard of care

Cost-effectiveness considerations

Generalisability of the cost comparison

The dosing schedule of bevacizumab reflects the proposed dosing in NHSScotland. Regional prescribing guidelines were used to calculate dosage of other chemotherapy regimens. NHSScotland PAS and national framework prices for medicines were considered in confidence to increase the generalisability of the net costs. In addition, the NHSScotland procurement database was used to adjust medicine acquisition costs of bevacizumab to reflect the most frequently used biosimilars across NHS Boards in Scotland (accessed April 2025).

Limitations of the cost comparison

There was no published cost-effectiveness analysis for the proposed use and cost-effectiveness is not known.

Due to an absence of cost-utility analysis, the analysis only compared costs. The evidence supporting clinical benefit of bevacizumab given in combination with chemotherapy in this patient population has been summarised in Section 3. An estimate of cost-effectiveness can be made by modelling the benefits over a longer period and comparing with costs. However, due to absence of long-term costs and health outcomes, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

Duration of treatment may be lower in proposed patient population

While assumptions considered clinical trial data and regional prescribing guidelines, dosage and duration may differ due to multiple factors like tolerance and disease progression. NHSScotland

real-world data for second-line treatments in the proposed patient population could not be analysed due to data limitations. However, the median duration from first-line use indicates it is likely lower than three months, suggesting that the base-case estimate for second-line could be slightly overestimated.

Summary

The cost-comparison indicated that bevacizumab plus chemotherapy is a cost-increasing intervention compared to NHSScotland SOC for patients with metastatic colorectal cancer in the second-line setting. However, in the absence of a cost-effectiveness analysis, it is difficult to quantify treatment benefits in relation to costs and the actual cost-effectiveness remains unknown.

8. Council Review | Cost-Effectiveness Evaluation

After considering all the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider additional relevant information including service impact and estimated net medicines budget impact under the Decision-making Framework for Value Judgements.

9. Service Impact

Bevacizumab is expected to have a significant service impact. It requires an additional intravenous infusion, resulting in increased chair time and pharmacy time when added to standard chemotherapy regimens. It may also extend treatment duration, particularly when continued as maintenance therapy with capecitabine or fluorouracil. It also introduces additional monitoring requirements during clinic visits, including urine dipstick testing, blood pressure monitoring and side effect management.

10. Budget Impact

Patient uptake

According to SACT data, it was estimated that 536 new patients receive first-line treatment for metastatic lower gastrointestinal cancer annually across Scotland. Based on clinical opinion and NHSScotland real-world data, approximately 40% to 50% would be eligible for second-line treatment. Among them, 75% would be eligible for the proposed bevacizumab plus chemotherapy regimen, excluding patients with contraindication to bevacizumab and those who may receive encorafenib plus cetuximab for cancer with a BRAF mutation or immunotherapy for MSI-H cancer. Therefore, the annual patient uptake for bevacizumab plus chemotherapy in second line for the proposed patient population was estimated to be around 160 to 200 patients per year in Scotland. The higher annual patient uptake was explored in Scenario 2 (Table 4). The uptake is assumed to remain constant in subsequent years. First-line bevacizumab was assessed independently of

second-line bevacizumab. Support of first-line bevacizumab use would be expected to reduce the eligible population for second-line treatment. Discontinuation and mortality rates were not included. The base case budget impact is presented using the lower estimate. NHSScotland real world data showed that 52% of metastatic colorectal cancer patients in the SACT database were prescribed a subsequent SACT after first line SACT. This was explored in Scenario 1 (Table 4).

Per patient medicine cost and treatment duration

These prices include VAT.

The medicine acquisition cost was used to determine net medicine budget impact. Confidential NHSScotland Patient Access Scheme (PAS) and National framework prices for medicines were used (accessed April 2025). The intervention was bevacizumab 5mg/kg every 14 days or 7.5mg/kg every 21 days, depending on the chemotherapy regimen used in combination.

The comparator consisted of four chemotherapy regimens commonly used in clinical practice across Scotland. The distribution of patients across these regimens was informed by clinical expert opinion and used to calculate a weighted average cost of the comparator. Treatments used in fewer than five percent of the patients were excluded from the analysis; the remaining proportions were then rescaled to maintain their relative ratios. The excluded regimens were single agent capecitabine or irinotecan, encorafenib plus cetuximab, nivolumab plus ipilimumab and raltitrexed-based chemotherapy. Therefore, the comparator comprised of CAPOX (37%), FOLFOX (18%), FOLFIRI (24%) and AFLIB plus FOLFIRI (21%), henceforth, referred as NHSScotland SOC.

The proposed chemotherapy regimens given in combination with bevacizumab are expected to follow the same proportions as observed in NHSScotland SOC with the exception of AFLIB plus FOLFIRI which would be replaced by bevacizumab plus FOLFIRI. Proportions were subsequently adjusted to account for this change.

Treatment duration for CAPOX with and without bevacizumab, FOLFOX with and without bevacizumab and FOLFIRI with bevacizumab were informed by the E3200 study, while FOLFIRI alone and AFLIB plus FOLFIRI treatment durations were informed by the VELOUR study. In the E3200 study, patients receiving FOLFOX-4 and bevacizumab had a median of 10 cycles, versus 7 cycles for FOLFOX-4 alone[16], while the VELOUR study reported median cycles of 9 and 8 in the AFLIB and placebo groups, respectively[23].

Comparator displacement

Based on feedback from clinical experts, introduction of bevacizumab would likely displace the following chemotherapy regimens: CAPOX, FOLFOX, FOLFIRI and AFLIB plus FOLFIRI, which together comprise the NHSScotland SOC.

Results

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Table 4: Budget impact analysis base case results (confidential price, including VAT)

	Year 1[a]
Acquisition cost	
Bevacizumab plus chemotherapy	CIC
NHSScotland SOC	CIC
Number of patients treated	160
Budget Impact	
Budget impact – Net medicine costs	CIC (budget increase)

CIC = commercial-in-confidence; SOC = standard of care; VAT = value added tax

[a] Year 1 results would represent subsequent years as it was assumed that patients or treatment duration would not continue to subsequent years.

Scenario considerations

Table 5: Scenario analyses (confidential prices, including VAT)

#	Scenario	Base case	Bevacizumab plus chemotherapy acquisition cost per patient	NHSScotland SOC acquisition cost per patient	Annual patient uptake	Budget impact – Net medicine costs
					Year 1[a]	
	-	Base case	CIC	CIC	160	CIC (budget increase)
Proportion of AFLIB plus FOLFIRI						
1	17%[b]	21%	CIC	CIC	160	CIC (budget increase, greater than base case)
Annual uptake						
2	200 patients	160 patients	CIC	CIC	200	CIC (budget increase, greater than base case)

CIC = commercial-in-confidence; SOC = standard of care; VAT = value added tax

[a] Year 1 results would represent subsequent years as it was assumed that patients or treatment duration would not continue to subsequent years.

[b] Following the adjustment of AFLIB plus FOLFIRI from 21% to 17%, the proportions of CAPOX, FOLFOX, and FOLFIRI were rescaled proportionally to maintain a total distribution of 100%.

Limitations

The variability in the duration of treatment with bevacizumab plus chemotherapy may lead to uncertainty in overall cost estimates. While assumptions considered clinical trial data and regional prescribing guidelines, dosage and duration may differ due to multiple factors like tolerance and disease progression. NHSScotland real-world data for second-line treatments in the proposed patient population could not be analysed due to data limitations. However, the median duration from first-line use indicates it is likely lower than 3 months, suggesting that the base-case estimate for second-line could be slightly overestimated.

The budget impact estimate is sensitive to the proportion of AFLIB plus FOLFIRI usage. NHSScotland real world analysis of subsequent treatments following first-line treatment in this patient population suggests that use of the AFLIB plus FOLFIRI regimen may be lower than clinical experts estimate. However, the real-world estimate may be underestimated due to caveats

surrounding the data analysis which made it challenging to ascertain which treatment was intended to be prescribed as second-line SACT[30]. This may have inflated the overall population receiving second-line SACT resulting in underestimating the proportion on AFLIB plus FOLFIRI. Due to higher medicine acquisition cost of on-patent AFLIB, reduction in proportion of AFLIB in the comparator arm could potentially increase the budget impact of bevacizumab plus chemotherapy arm. This was explored in Scenario 1 (Table 4).

Finally, NHSScotland real-world data showed that 52% of metastatic colorectal cancer patients in the SACT database were prescribed a subsequent SACT after first-line SACT. This was explored in Scenario 2 (Table 4)[30].

Summary

The use of bevacizumab plus chemotherapy is expected to increase the net medicines budget impact for this patient group when compared to NHSScotland SOC.

The Council considered the net medicines budget impact using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the budget impact using confidential pricing due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with PAS contract pricing.

11. Council Review | Overall Proposal Evaluation

After consideration of all relevant information under the Decision-making Framework for Value Judgements the Council made a decision to support this use.

12. Acknowledgements

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by