National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG123 Bevacizumab | Advice Document v 1.0|July 2025

Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first 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 and cost-effectiveness for bevacizumab in the proposed population.

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	First-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. It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.
Advice eligibility criteria	• First-line treatment of metastatic colorectal cancer • Patients unsuitable for epidermal growth factor receptor (EGFR) inhibitor therapy • 18 years of age or older

1. Current Management Context

Metastatic colorectal cancer symptoms, incidence and prognosis

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

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[2, 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[3]. The mean age of diagnosis with bowel cancer is 71 years[5]. Patients who are unsuitable for EGFR inhibitor therapy have a poorer prognosis, estimated at less than two years[6]. Unsuitability may be due to the presence of a KRAS or NRAS mutation, BRAF mutation, or right sided tumour.

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 and BRAF genes, 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[7, 8], BRAF mutation in 10% and MSI-H in 5%. If the primary tumour and metastases are resectable they can be removed with curative intent. Some patients may receive downstaging chemotherapy to try to reduce the cancer burden and achieve resectability.

Fluoropyrimidine (fluorouracil or capecitabine) forms the backbone of chemotherapy for metastatic colorectal cancer, typically combined with either oxaliplatin or irinotecan. Regimens include capecitabine, infusional fluorouracil, FOLFOX (fluorouracil, folinic acid, oxaliplatin), CAPOX (capecitabine, oxaliplatin), FOLFIRI (fluorouracil, folinic acid, irinotecan) and FOLFOXIRI (fluorouracil, folinic acid, oxaliplatin and irinotecan). Both irinotecan and oxaliplatin regimens are considered equally effective: toxicity profiles of the regimens are used to guide selection[9, 10].

When first treated for metastatic colorectal cancer, patients with left sided, RAS/BRAF wild type cancers are also eligible for the addition of EGFR targeted therapies, cetuximab or panitumumab, to their chemotherapy regimens. First line treatment for microsatellite instability (MSI) high/mismatch repair (MMR) deficient metastatic colorectal cancer will usually involve immunotherapy, with chemotherapy used in the second line setting[11].

Bevacizumab is licensed for use in combination with fluoropyrimidine-based chemotherapy for treatment of adult patients with metastatic carcinoma of the colon or rectum. 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[12, 13].

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 for the first-line treatment of colorectal cancer in patients unsuitable for EGFR inhibitor therapy[2, 14, 15]. 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[16].

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, first-line and metastatic. 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.

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

The key evidence supporting this proposal comes from four phase III multicenter, open label, randomised clinical trials[17-20]. Patients aged 18 years and older (20 to 75 in the WJOG4407G study) with a life expectancy of greater than three months, an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 1 (or 2 in the Hurwitz et al study) who had previously untreated, histologically confirmed, metastatic colorectal cancer were included in these trials. The trials included various chemotherapy backbones which will be described below in Table 1.

Table 1: Key studies and treatment regimen details[a]

	Regimen 1	Regimen 2

Hurwitz et al 2004[21]	**IFL plus bevacizumab** Bevacizumab 5mg/kg BW every 2 weeks Irinotecan 125mg/m^2 BSA Bolus fluorouracil 500mg/m^2 BSA Leucovorin 20mg/m^2 BSA Once weekly for 4 weeks: cycle repeated every 6 weeks	**IFL plus Placebo** Placebo (every 2 weeks) Irinotecan 125mg/m^2 BSA Bolus fluorouracil 500mg/m^2 BSA Leucovorin 20mg/m^2 BSA Once weekly for 4 weeks: cycle repeated every 6 weeks
Saltz et al 2008[18]	**Bevacizumab plus CAPOX or FOLFOX-4** Bevacizumab 7.5mg/kg day 1 of 3-week cycle (CAPOX) or Bevacizumab 5mg/kg day 1 of 2-week cycle (FOLFOX-4) <u>CAPOX</u> Oxaliplatin 130mg/m^2 day 1 of 21-day cycle Oral capecitabine 1000mg/m^2 BD on days 1 through 14 of 21-day cycle <u>FOLFOX-4</u> Oxaliplatin 85mg/m^2 Leucovorin 200mg/m^2 Bolus fluorouracil 400mg/m^2 Continuous infusion of fluorouracil 600 mg/m^2 over 22 hours on Day 1 and Day 2 of 14-day cycle	**CAPOX or FOLFOX-4 plus placebo** Placebo (every 2 weeks) <u>CAPOX</u> Oxaliplatin 130mg/m^2 day 1 of 21-day cycle Oral capecitabine 1000mg/m^2 BD on days 1 through 14 of 21-day cycle <u>FOLFOX-4</u> Oxaliplatin 85mg/m^2 Leucovorin 200mg/m^2 bolus Fluorouracil 400mg/m^2 Continuous infusion of fluorouracil 600 mg/m^2 over 22 hours on Day 1 and Day 2 of 14-day cycle
WJOG4407G[20]	**FOLFIRI plus bevacizumab** Bevacizumab 5 mg/kg on day 1 of each 14-day cycle <u>FOLFIRI</u> Irinotecan 150 mg/m^2 l-leucovorin 200 mg/m^2 Bolus fluorouracil 400mg mg/m^2 Continuous infusion of fluorouracil 2400 mg/m^2 over 48h	**mFOLFOX-6 plus bevacizumab** Bevacizumab 5 mg/kg on day 1 of each 14-day cycle <u>mFOLFOX-6</u> Oxaliplatin 85 mg/m^2 l-leucovorin 200 mg/m^2 Bolus fluorouracil 400mg mg/m^2 Continuous infusion of fluorouracil 2400 mg/m^2 over 46h
BECOME[19]	**mFOLFOX-6 plus bevacizumab**	**mFOLFOX-6 alone** <u>mFOLFOX-6</u>

	Bevacizumab 5 mg/kg on day 1 of each 14-day cycle <u>mFOLFOX-6</u> Oxaliplatin 85mg/m^2 l-leucovorin 200 mg/m^2 IV bolus fluorouracil 400mg mg/m^2 Continuous infusion of fluorouracil 2400 mg/m^2 over 48h on day 1 of each 14-day cycle	Oxaliplatin 85mg/m2 l-leucovorin 200 mg/m2 IV bolus fluorouracil 400mg mg/m2 Continuous infusion of fluorouracil 2400 mg/m2 over 48h on day 1 of each 14-day cycle

Key: IFL: irinotecan, fluorouracil and leucovorin; BSA: body surface area; BW: body weight; IV: intravenous
[a]all medicines were administered via intravenous infusion or injection unless otherwise stated

Evidence supporting irinotecan, fluorouracil and leucovorin (IFL) in combination with bevacizumab

Hurwitz et al[21] randomised patients on a 1:1:1 basis to receive either IFL plus bevacizumab (n=402), IFL (irinotecan, fluorouracil and leucovorin) plus placebo (n=411) or fluorouracil, leucovorin plus bevacizumab (this arm is not a relevant comparator and only the comparison between IFL plus bevacizumab and IFL plus placebo will be described here). Patients were stratified by study centre, baseline ECOG performance status (0 versus 1), site of primary disease (colon versus rectum) and number of metastatic sites (one versus more than one). The primary outcome was the duration of overall survival from time of randomisation (OS). Secondary outcomes include progression free survival (PFS), objective response rate (ORR), duration of response (DOR) and quality of life. Response and progression were determined using the response evaluation criteria in solid tumors (RECIST v1.0) (2000).

Evidence supporting CAPOX or FOLFOX-4 in combination with bevacizumab

Saltz et al[18] randomised patients on a 1:1 basis to receive either CAPOX or FOLFOX-4 plus bevacizumab (n=699) versus CAPOX or FOLFOX-4 plus placebo (n=701). Patients were stratified by region, ECOG performance status, liver as a metastatic site, alkaline phosphatase level and number of metastatic sites. The primary outcome was PFS defined as time from random assignment to the first documentation of investigator assessed progressive disease or death from any cause. Secondary outcomes include OS, response rate (RR), DOR and time to treatment failure (TTF). Response and progression were determined by RECIST v1.0.

Evidence supporting mFOLFOX-6 in combination with bevacizumab

Two studies examined the use of bevacizumab in combination with mFOLFOX-6[19, 20]. The WJOG4407G[20] study, designed as a non-inferiority study, randomised Japanese patients on a 1:1 basis to receive FOLFIRI plus bevacizumab (n=197) versus modified FOLFOX-6 (mFOLFOX-6) plus bevacizumab (n=198). Patients were stratified by institution, postoperative adjuvant chemotherapy (yes/no) and metastatic organs (liver only versus liver and other organs). The primary outcome was PFS defined as the interval from the date of randomisation to the date of confirmed progressive disease or death from any cause, whichever came first. Secondary

endpoints include OS, TTF, RR, the proportion of patients receiving curative resection and quality of life. Response and progression were determined by RECIST v1.0.

The BECOME[19] study randomised patients on a 1:1 basis to receive mFOLFOX-6 plus bevacizumab (n=121) versus mFOLFOX6 alone (n=120). The primary outcome was the actual conversion rate to radical resection for liver metastases. Response was assessed by a blinded multidisciplinary team every four cycles for up to 12 cycles. Secondary outcomes include tumor response, OS and PFS. Response and progression were determined by RECIST v1.1.

Summary of results from the included studies

Across all four studies the baseline characteristics were similar (Table 2). The median age of patients ranged from 58 to 63 years. Only the Hurwitz study included patients with an ECOG PS of 2[21], however these accounted for less than 1% of patients recruited. The proportion of patients with an ECOG PS of 1 ranged from 19% to 44%.

Table 2: Baseline characteristics of patients in the included studies

	Hurwitz et al 2004[21]		Saltz et al 2008[18]		WJOG4407G[20]		BECOME[19]	
	IFL plus bev n=402	**IFL n=411**	**CAPOX or FOLFOX-4 plus bev n=699**	**CAPOX or FOLFOX-4 plus placebo n=701**	**FOLFIRI plus bev n=197**	**mFOLFOX 6 plus bev n=198**	**mFOLFOX 6 plus bev n=121**	**mFOLFOX 6 n=120**
Median age (years)	Mean 59	Mean 59	60	60	63	62	58	59
% male	59	60	60	56	53	62	65	66
ECOG % 0 1 2	 58 41 <1	 55 44 <1	 58 42 <1	 60 40 0	 81 19 0	 78 22 0	 69 31 0	 62 38 0

Key: Bev: bevacizumab; ECOG: European cooperative oncology group. Refer to Table 1 for treatment regimen details.

Median follow-up was only reported in three trials and ranged from 28 months to 37 months[18-20]. Three studies compared chemotherapy with bevacizumab versus chemotherapy with placebo: PFS and OS in these studies was greater in the study arms receiving the bevacizumab-containing regimens[18, 19, 21]. The PFS and OS results in the Hurwitz[21] and BECOME[19] studies were statistically significant, while only the PFS in the Saltz[18] study was significant, with only a numerical difference in favor of the bevacizumab-containing arm for OS. In the WJOG4407G study both arms included bevacizumab, comparing FOLFIRI to mFOLFOX-6, and there was no evidence of a significant difference in PFS or OS in this study. A numerical difference favoured bevacizumab in combination with FOLFIRI (Table 3)[20]. Despite the different chemotherapy backbone regimens used in each study, all outcomes were improved in the bevacizumab containing arms.

Table 3: Key efficacy results from the included studies

	Hurwitz et al 2004[21]		Saltz et al 2008[18]		WJOG4407G[20]		BECOME[19]	
	IFL plus bev N=402	**IFL N=411**	**CAPOX or FOLFOX-4 plus bev n=699**	**CAPOX or FOLFOX-4 plus placebo n=701**	**FOLFIRI plus bev n=197**	**mFOLFOX 6 plus bev n=198**	**mFOLFOX 6 plus bev n=121**	**mFOLFOX 6 n=120**
Median follow up, months	NR		27.6	29.3	32.6		37	
Progression free survival								
Events, n	NR	NR	513	547	152	160	109	112
Median, months (95% CI)	10.6	6.2	**9.4**	**8.0**	12.1 (11 to 14)	10.1 (9.9 to 12)	9.5 (8.6 to 10.4)	5.5 (5.1 to 6.1)
HR (95% CI)	0.54 (0.37 to 0.78)[b]		**0.83 (97.5% CI 0.72 to 0.95)[a]**		**0.90 (0.72 to 1.13)**		0.49 (0.38 to 0.65)[b]	
Overall survival								
Events, %	NR	NR	420	455	142	146	74	88
12m survival	74%	63%	NR	NR	NR	NR	94%	76%
Median, months (95% CI)	**20.3**	**15.6**	21	20	31.4 (28 to 36)	30.4 (27 to 35)	26 (20 to 31)	20 (17 to 24)
HR (95% CI)	**0.66 (0.52 to 0.85)** [b]		0.89 (97.5% CI 0.76 to 1.03)		0.99 (0.78 to 1.25)		0.71 (0.52 to 0.97) [a]	
Response rate								
Response rate %	45%	35%	47%	49%	64%	62%	66%	44%
OR	NR		0.9 (97.5% CI 0.76 to 1.03)		NR		NR	
Other outcomes								
Underwent curative resection	NR	NR	8.4%	6.1%	10%	9%	**23%[a]**	**7%[a]**

Key: NR: not reported; CI: confidence interval; HR: hazard ratio; OR: odds ratio. Refer to Table 1 for treatment regimen details.

Primary outcomes are in bold font

[a] significant at <0.05 level

[b] significant at <0.01 level

Supportive evidence

One study was identified as supportive of the key evidence. AVEX was an open label phase 3 randomised controlled trial that examined the efficacy and safety of bevacizumab (7.5 mg IV every 3 weeks) with oral capecitabine compared with capecitabine alone in elderly patients with previously untreated metastatic colorectal cancer[22]. Patients were randomised 1:1 and stratified by ECOG PS (0 to 1 versus 2) and geographical region. The primary outcome was PFS defined as the time from random assignment to disease progression or death of any cause, whichever

occurred first. Secondary outcomes include safety, response, and overall survival. Baseline characteristics were balanced between the treatment arms (n=140 in each arm), median age was 76 years. In the bevacizumab plus capecitabine arms 41% and 7% had an ECOG of 1 and 2 respectively. In the capecitabine arm alone 48% and 8% had an ECOG PS of 1 and 2 respectively. After a median follow up of 24.8 months (IQR 15.1 to 37.7) in the bevacizumab plus capecitabine arm and 21.6 months in the capecitabine only arm median PFS was 9.1 months and 5.1 months (HR: 0.53 95% confidence interval [CI] 0.41 to 0.91) in the respective arms. Overall response rate was reported in 19% versus 10% in the bevacizumab plus capecitabine arm versus capecitabine arm respectively. At data cutoff 75 patients in both groups had died, median OS was 20.7 months in the bevacizumab plus capecitabine arm versus 16.8 months in the capecitabine arm (HR 0.79 95% CI 0.57 to 1.09)[22].

Patient reported outcomes

One study reported quality of life data. The WJOG4407G study collected quality of life (QoL) data using the functional assessment of cancer therapy – colorectal (FACT-C) and FACT/GOG-Neurotoxicity version 4 at baseline, and at 3, 6 ,9 ,12 and 18 months. There was a slight trend for improved QoL in the FOLFIRI plus bevacizumab arm over the FOLFOX plus bevacizumab arm, although none were significant, and in both groups the QoL decreased over time[20].

Safety evidence

This is an on-label use which has been considered by the UK medicines regulator to have an acceptable safety profile. Bevacizumab is associated with a number of adverse events which are summarised in Table 4.

Table 4: grade 3 or greater adverse events

	Hurwitz et al 2004		Saltz et al 2008		WJOG4407G		BECOME 2020	
	IFL plus bev N=402	IFL N=411	CAPOX or FOLFOX-4 plus bev N=694	CAPOX or FOLFOX-4 plus placebo N=675	FOLFIRI plus bev n=195	mFOLFOX 6 plus bev n=198	mFOLFOX 6 plus bev n=121	mFOLFOX 6 n=120
Total grade ≥3 adverse events %	85%	74%	80%	75%	NR	NR	40%	27%
Thromboembolic events (venous and arterial)	19%[a]	16%[a]	10%	6%	-	-	6.6%	5%
Proteinuria	0.8%	0.8%	<1%	-	-	-	9.9%	3.3%
Gastrointestinal perforation	1.5%	-	<1%	<1%	2%	1%	NR	NR
Hypertension	11%	2.3%	4%	1%	3%	6%	8.3%	2.5%
Leukopenia	37%	31%	NR	NR	11%	5%	14%	12%
Diarrhea	32%	25%	NR	NR	9%	5%	NR	NR
Hemorrhage	3.1%	2.5%	NR	NR	-	1%	3.3%	1.7%

[a]any grade
Bev: bevacizumab, NR: not reported

Quality Appraisal

The four studies included were all phase III randomised controlled trials and were all judged to have a low risk of bias with some minor concerns. All studies used an open-label design which may lead to outcome detection bias especially when assessing subjective outcomes. All four studies did not report on their allocation concealment and all but one study failed to report on whether outcome assessment was blinded. The four studies applied a version of the RECIST criteria when assessing response and progression, which may protect against assessment bias.

Clinical effectiveness considerations

Bevacizumab has been shown to improve OS, PFS and tumour resectability when used in combination with various chemotherapy regimens.

Four studies (Hurwitz et al, Saltz et al, AVEX and BECOME) explored the efficacy of bevacizumab when added to various chemotherapy regimens and met their primary outcomes[18, 20-22]. Together the studies showed the addition of bevacizumab produced statistically significant improvements in PFS, OS and conversion rate to radical resection.

There is variation in the reported magnitude of benefit associated with the addition of bevacizumab, this may be due to variation in accompanying chemotherapy and variation in continuing bevacizumab until progression

The variation in the magnitude of benefit with the addition of bevacizumab across the studies may be due to differences in the efficacy of bevacizumab when combined with different chemotherapy regimens. It may also be due to the early discontinuation of bevacizumab, prior to progression, coinciding with early chemotherapy discontinuation in regimens containing oxaliplatin (which characteristically causes cumulative neurotoxicity). In the Saltz study, which showed the smallest PFS and OS gains of the three studies, approximately 70% of patients discontinued FOLFOX-4 or CapOx plus bevacizumab prior to progression[18]. It is hypothesised that this early discontinuation of bevacizumab in the Saltz study may have contributed to the reduced magnitude of benefit, compared to regimens where treatment was continued until progression. The WJOG4407G study had similar rates of early discontinuation in both groups and found bevacizumab plus FOLFIRI to be non-inferior to bevacizumab plus mFOLFOX6[20]. Furthermore, the benefit of continuing bevacizumab to progression, in combination with fluoropyrimidine alone after oxaliplatin discontinuation, was confirmed in the CAIRO study[23].

Several meta-analyses have shown a consistent benefit of first-line treatment with bevacizumab when added to chemotherapy regimens, including in RAS mutant patients and those with right-sided tumors, though effect size varies due to differences in included studies and statistical analyses[24-26]

There are some generalisability concerns from the key studies.

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 Saltz and Hurwitz studies included younger patient populations with a median age of around 60 years and better performance status which may reduce the generalisability of the results to the NHSScotland population. The AVEX study, which examined the addition of bevacizumab in combination with capecitabine in an older patient population, may provide some reassurance regarding the efficacy and tolerability of bevacizumab in older patients and those with poorer performance status (approximately 50% had a PS of 1 or 2).

Chemotherapy regimens have evolved since the Hurwitz and Saltz studies, with changes to the dosing and administration of fluorouracil and folinic acid. This evolution may affect the generalisability of the results, particularly for the IFL regimen used in the Hurwitz study, which is significantly different to currently used dosing regimens. The WJOG4407G and BECOME studies may provide some reassurance that the proposed dosing is at least as effective as the dosing regimens from the Hurwitz and Saltz studies with a more favourable safety profile.

In the BECOME study patients' cancers had to be RAS mutated to be included, with liver-only metastatic disease. Patients with RAS mutated cancers are similar to the proposed first-line population, that is, not suitable for EGFR inhibitor therapy. The median age of participants was 58 years, although a younger population would be expected for downstaging patients. Response assessment was blinded; however, as a single-center study in China, the results may be less generalisable to the NHSScotland population.

Differences in subsequent treatment profiles across the studies may also affect the generalisability in terms of overall survival.

Bevacizumab may also be used with FOLFOXIRI (containing fluorouracil, folinic acid, oxaliplatin, and irinotecan) in the first line where the most efficacious regimen is needed, such as for potential downstaging to allow for curative treatment. The TRIBE2 study showed that bevacizumab and FOLFOXIRI can be more effective than sequential treatment with oxaliplatin and irinotecan regimens plus bevacizumab[27]. However, no studies have directly compared FOLFOXIRI with and without bevacizumab, so the benefit of bevacizumab in this combination is uncertain.

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

Across the studies, 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[1].

The addition of bevacizumab to first-line chemotherapy may affect the second-line treatment pathway

If bevacizumab becomes routinely available in the first-line setting, the eligible population for second-line treatment with aflibercept in combination with FOLFIRI may be reduced[28].

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 PFS, resectability and, in some studies, to also improve overall survival.

6. Council Review | Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and harms, the Council were satisfied with the clinical effectiveness of bevacizumab in combination with fluoropyrimidine-based regimen.

7. Economic Evidence Review Summary

Economic Overview

Several economic evaluations were identified in the literature search, providing pairwise comparisons of bevacizumab in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in adult patients with metastatic colorectal cancer. The majority of these were from a non-UK perspective. One publication was commissioned by the NHS Health Technology Assessment (HTA) Programme to inform the National Institute for Health and Clinical Excellence's (NICE) Technology Appraisal of bevacizumab in the treatment of metastatic colorectal cancer in England and Wales in 2007[29]. The corresponding NICE technology appraisal of bevacizumab was informed by two manufacturers' submitted cost-effectiveness models and the two models developed by the NHS HTA programme[13].

As part of our assessment review, we received one of the two models from the manufacturer of the bevacizumab originator product. The primary objective of the analysis was to evaluate the cost-effectiveness of bevacizumab in combination with chemotherapy (bevacizumab plus CAPOX or FOLFOX-4) compared to chemotherapy (CAPOX or FOLFOX-4) alone for patients with inoperable locally advanced or metastatic colorectal carcinoma who have not previously received systemic treatment for metastatic disease.

Type of economic evaluation

The preferred approach was to adapt the manufacturer's original model, to include inputs in line with recent data. The key changes to the model are summarised under the model adaptation section below. A cost-utility analysis was used for the economic evaluation. A simple state transition Markov model was developed in which patients transition between three health states: progression-free, progressed disease and death. The clinical data were derived from Saltz et al 2008[18]. The model used non-treatment dependent, health state-specific utility values (HSUV) of 0.95 for progression-free disease, 0.58 for progressive disease and 0.00 for death, derived from a 1997 study which explored the quality of life of patients with colorectal cancer[30]. The costs and outcomes were modelled over an 8-year time horizon, with the average age of 60 years for the cohort entering the model. The perspective of the economic evaluation was indicated to be for the NHS in England and Wales and relevant costs were sourced from the literature.

Population, intervention, comparator and outcomes

The population used in the model was patients with inoperable locally advanced or metastatic colorectal carcinoma who did not previously receive systemic treatment for metastatic disease. The intervention was bevacizumab in combination with chemotherapy (bevacizumab plus CAPOX or FOLFOX-4). The comparator was chemotherapy (CAPOX or FOLFOX-4) alone. Clinical outcomes used in the model were OS, PFS and grade 3 to 4 adverse events. Outcomes of the economic model were survival (life years gained) and quality adjusted life years (QALYs).

Model adaptation

The original model was adapted to reflect clinical practice in NHSScotland and updated costs for healthcare services. Based on clinical expert opinion, the proportion of CAPOX and FOLFOX-4 was assumed to be 90% and 10% respectively in both the backbone chemotherapy with bevacizumab and comparator arms.

The administration costs for intravenous medicines and management of adverse events were updated to NHS reference costs 2024/25 (accessed May 2025). Where a suitable procedure code was not identified, the cost was corrected for inflation using consumer price inflation index (CPI) for health issued by the Office of National Statistics (ONS) (last updated in March 2025). The background mortality was updated to reflect age-specific general population rate of death in Scotland using ONS National Life Tables of Scotland 2021-2023 (accessed May 2025).

Finally, the uncertainty was explored in sensitivity analysis (Table 5). These included alternate proportions of chemotherapy based on the NHSScotland real world evidence (60% CAPOX and

40% FOLFOX-4), utility values from other published sources, use of pre-filled infusion bags, and exclusion of administration and adverse event management costs.

Costs

Costs included were medicine acquisition, medicine administration costs for intravenous medicines, costs associated with central venous access device (CVAD) placement, maintenance and removal, and adverse event management costs.

The medicine acquisition costs are based on the unit price of solution for infusion vials. Some NHS Boards may use pre-filled compounded aseptic medicines, which was explored in a separate Scenario 2. 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's procurement database (accessed March 2025).

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). 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, while all cycles of fluorouracil (FOLFOX-4 regimen) and oxaliplatin (CAPOX regimen) involved administration of complex parenteral chemotherapy. The dose and duration of treatment was sourced from Saltz study[18].

The costs associated with CVAD placement, maintenance and removal were based on CVAD usage reported in the Saltz study[18]. The costs were updated using NHS reference costs 2023-25 (accessed May 2025).

The costs associated with managing Grade 3 and 4 adverse events were based on rates observed in the Saltz study[18]. The unit costs for adverse events were determined based on clinical opinion of estimated average duration of hospital stay in NHS Scotland and corresponding hospital procedures codes available in the NHS reference costs 2023-25 database (accessed May 2025).

Key results

The Council considered results using NHSScotland PAS or National Framework prices in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence pricing contracts.

Sensitivity analysis

Scenario analyses were conducted to explore uncertainty in key model assumptions (Table 5). Several limitations remain and are elaborated in the Limitations sub-section below. Most scenarios resulted in higher ICERs. However, the clinical data underpinning the model is considered conservative, which may underestimate the true clinical benefit of bevacizumab plus chemotherapy compared to chemotherapy alone. Due to limitations in model

functionality, it was not possible to test more optimistic assumptions such as alternate survival curves. Moreover, the utility values applied in the model are associated with uncertainty. This introduces potential overestimation of QALY gains. While underestimating life-years gained could bias the modelled clinical benefit against bevacizumab plus chemotherapy, overestimating utility values could offset this benefit to an unknown degree. Therefore, the overall clinical benefit remains uncertain. A range of scenarios including alternative approaches to utility values and administration costs were explored, and the ICER remained relatively stable.

Table 5: Scenario analysis results (confidential price, excluding VAT)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. LYG	Incr. QALYs	ICER (£/QALY) [a]
	Base case	-	-	CIC	CIC	CIC	CIC
1	Proportion of chemotherapy	CAPOX 90% FOLFOX-4 10%	CAPOX 60% FOLFOX-4 40%	CIC	CIC	CIC	CIC Increase
2	Medicine acquisition of bevacizumab and oxaliplatin	Price per vial for infusion	Price per pre-filled compounded aseptic bag	CIC	CIC	CIC	CIC Increase
3	Administration costs	Included	Excluded	CIC	CIC	CIC	CIC Decrease
4	CVAD costs	Included	Excluded	CIC	CIC	CIC	CIC Decrease
5	AE management costs	Included	Excluded	CIC	CIC	CIC	CIC Decrease
6a	Health state specific utilities (source)	PF= 0.95 PD= 0.58 (Petrou et al. 1997)	PF= 0.77 (NICE TA439); PD= 0.58 (Petrou et al. 1997)	CIC	CIC	CIC	CIC Increase
6b			PF= 0.77; PD= 0.66 (NICE TA439)	CIC	CIC	CIC	CIC Increase
6c			PF= 0.77 (NICE TA439); PD= 0.73 (NICE TA709)	CIC	CIC	CIC	CIC Increase

Abbreviations: AE = adverse event; CIC = commercial-in-confidence, CVAD = central venous access device; Incr. = Incremental; ICER = incremental cost-effectiveness ratio; OS = overall survival; PF = progression-free; PD = progressed disease; LYG = life years gained; QALY = quality-adjusted life year.
[a]Increase or decrease relative to base case.

Cost-effectiveness considerations

Generalisability of the cost effectiveness

The manufacturer's model was adapted to include relevant costs for NHSScotland. Wherever appropriate NHS reference prices were not available, inflation adjustments were made using CPI index rates specific to health category (accessed Mar 2025). Further adaptations, outlined in model adaptation sub-section, improved the external validity to NHSScotland.

Limitations of the cost effectiveness

Uncertainty around the clinical evidence used in the model

The median PFS and OS gain across various studies ranged from 1.4 to 5.5 months and 1.0 to 6.0 months, respectively (Table 3). The model was informed by clinical outcomes from the Saltz study[18], the limitations of which, in the context of this proposal, are described in the Clinical Effectiveness section above. These include a different chemotherapy regimen to what has been proposed (FOLFOX-4 versus mFOLFOX-6) and early discontinuation of bevacizumab. The model extrapolated PFS and OS data from the Saltz study and estimated a mean life year gained of 0.20 (equivalent to 2.42 months). Clinical evidence from the BECOME and Hurwitz studies show trends towards a greater relative benefit for bevacizumab plus chemotherapy compared to chemotherapy alone[19, 21]. This may suggest that the survival data used to inform the QALY gain over the model's time horizon may underestimate the survival benefit with bevacizumab. Alternate survival curve extrapolations could not be explored in the model due to absence of such functionality.

Health state utility values (HSUVs) lack external validity

The model included utility values from an old publication by Petrou et al[30] which may lack generalisability to the proposed patient population. Evidence from other cost-effectiveness studies in similar patient populations suggests that progression-free HSUVs for patients on first-line treatment for metastatic colorectal cancer could range from 0.77 to 0.85 which is much lower than the value used in the model[31, 32]. Alternative utility values for progressed disease were reported in NICE TA439 of cetuximab for the first-line treatment of previously untreated metastatic colorectal cancer and NICE TA709 of pembrolizumab for the first-line treatment of adults with MSI-H or dMMR colorectal cancer (0.66 and 0.73, respectively)[31, 32]. These are higher than what is used in the model base case. In addition, utility decrements associated with adverse events were not included in the model. Therefore, the resulting QALY gain in the model may be overestimated. A combination of HSUVs from published literature was explored in Scenarios 6a-c which increased the baseline ICERs.

Cost-effectiveness of bevacizumab plus capecitabine alone or bevacizumab plus irinotecan-based chemotherapy remains uncertain

Based on clinical expert opinion, the current standard of care in this patient population includes single agent capecitabine (17%), doublet regimens like CAPOX (50%), FOLFOX (15%) or FOLFIRI (10%), and in a minority of cases (8%) the triplet FOLFOXIRI regimen or raltitrexed-based regimens

may be used. The overall proportion of doublet chemotherapy aligned with NHSScotland real world data with slightly different distribution of the various doublet regimens[33]. An alternative distribution of CAPOX and FOLFOX-4, used to calculate treatment-related costs, was explored in Scenario 1.

The cost-effectiveness model included CAPOX and FOLFOX-4 as chemotherapy options, which limits the generalisability of the results to other chemotherapy options, including single agent capecitabine and FOLFIRI. The AVEX study demonstrated improved PFS for bevacizumab combined with capecitabine compared to capecitabine alone. The WJOG4407G study[20] suggests there is no evidence of a significant difference in PFS and OS between the bevacizumab plus FOLFIRI regimen and the bevacizumab plus FOLFOX regimen. [22]. However, in the absence of cost-effectiveness analyses, the cost-effectiveness of bevacizumab plus capecitabine and bevacizumab plus irinotecan-based regimens remains uncertain.

Baseline characteristics in the model may be different compared to clinical practice in Scotland

The starting age in the model was determined to be 60 years, based on baseline age reported in the Saltz study[18]. This is lower than the average age observed across Scotland based on NHSScotland real world data for first line patients receiving SACT (median age 68 (57 – 73) years)[33]. Based on clinical expert opinion, the age at the start of treatment is unlikely to affect clinical response. However, it could affect the choice of backbone as single agent capecitabine is preferred for older and frailer patients.

Duration of treatment used in the model may differ from real-world setting in Scotland

Clinical practice in Scotland has evolved since the publication of Saltz study in 2008[18]. The use of mFOLFOX-6 has replaced the FOLFOX-4 regimen. The key difference is that, in addition to the bolus treatments of, fluorouracil and folinic acid for both regimens on day 1, the mFOLFOX-6 regimen involves a 46 hour continuous infusion of a higher dose of fluorouracil (delivered via a portable infusion device through a peripherally inserted central catheter or central line, at home) compared to FOLFOX-4 which involves an inpatient stay for two 22-hour infusions of a lower dose of fluorouracil. Therefore, mFOLFOX-6 regimen involves fewer administrations, which could reduce costs and resource utilisation. The WJOG4407G and BECOME studies may provide some reassurance that the mFOLFOX-6 is at least as effective as the FOLFOX-4 regimen reported in the Saltz study with a more favourable safety profile[18]. Although this may improve cost-effectiveness, its impact on the ICER was not explored in this analysis.

In addition, findings from the CAIRO study[23] suggest that continuing bevacizumab to progression, in combination with fluoropyrimidine alone after oxaliplatin discontinuation, may provide clinical benefit. This implies that a proportion of patients may receive longer maintenance treatment in the bevacizumab arm, potentially increasing treatment costs. The clinical benefit of this approach has not been modelled and cost-effectiveness in the proposed setting remains uncertain, However, NHSScotland real world data reported a median duration of approximately three months for first-line use, suggesting that patients continuing prolonged maintenance may be a small subgroup[33].

Uncertainty in subsequent treatment costs

There is uncertainty around subsequent treatments following first-line bevacizumab plus chemotherapy versus chemotherapy alone. The cost-comparison analysis does not include potential costs, or cost avoidance, of these treatments. The direction of impact remains unknown.

Summary

There is a high degree of uncertainty in the magnitude of the overall QALY gain. On one hand, the modelled life-years gained may underestimate the clinical benefit of bevacizumab plus chemotherapy (which has not been possible to explore); on the other, the utility values used may be overestimated (explored in scenario analyses), potentially offsetting this benefit. As a result, the true cost-effectiveness remains uncertain, with clinical benefits potentially inadequately captured in the model.

This analysis should be considered within the context described in the document 'Health Economic Considerations in NCMAG Decision Making'[34]. In some specific situations NCMAG may exercise greater flexibility in its decision making to allow consideration of additional factors, including uncaptured benefits and non-health factors. These may allow NCMAG to accept either more uncertainty in the health economic case or a higher cost per QALY.

8. Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council were satisfied with the cost effectiveness of the proposed use.

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

The change in treatment will increase the budget impact for this patient group. The figures considered were based on PAS or NHSScotland National Framework contract prices for bevacizumab and other chemotherapy regimens. The proportion of patients receiving any of the four most commonly used chemotherapy regimens in NHSScotland (single agent capecitabine (18%), doublet regimens like CAPOX (54%), FOLFOX (16%) or FOLFIRI (11%) was assumed to be the same when used alone or in combination with bevacizumab and was based on clinical expert opinion. The duration of therapy for bevacizumab in combination with chemotherapy was longer

than the respective chemotherapy regimen given alone based on clinical evidence. The cost per patient per year was weighted by the estimated proportion of patients who may get any of the chemotherapy regimens. These figures are based on an estimated annual uptake of 290 patients in the first year of treatment. Some patients may carry over to subsequent years as they may require a longer maintenance treatment with bevacizumab.

NCMAG is unable to publish the budget impact 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 impact with the national framework contract pricing.

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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