Use of bevacizumab in the treatment of metastatic colorectal cancer

The Cancer Drugs Fund may allow more patients in England access to clinically effective cancer therapies. In this article oncologists already familiar with the clinical evidence, and experienced in treating with bevacizumab, share practical recommendations on optimal first-line use of this treatment for metastatic colorectal cancer.

A number of monoclonal antibodies, which act as biological targeted therapies, are licensed in the UK in combination with, or after failure of chemotherapy, in the management of metastatic colorectal cancer (Amgen Ltd, 2011; Merck Serono, 2011; Roche Products Ltd, 2011). However, until the introduction of the Cancer Drugs Fund (Department of Health, 2010a) in England, these treatments were uncommonly used as they were not approved by the National Institute of Health and Clinical Excellence. Bevacizumab has been reviewed twice by National Institute of Health and Clinical Excellence (2007, 2010). In both cases bevacizumab was not recommended for the treatment of metastatic colorectal cancer because of cost effectiveness and so first-hand clinical experience of integrating bevacizumab into the metastatic colorectal cancer treatment pathway remained limited.

The Cancer Drugs Fund was prompted by the findings of a report entitled *Extent and causes of international variations in drug usage* which highlighted that the UK compared unfavourably against other developed nations in terms of its uptake of newer cancer drugs (Richards, 2010). The UK spend on cancer drugs within 5 years of their license is less than half of the mean spend on these cancer drugs by countries with similar gross domestic product and health-care expenditure, such that the UK was ranked 12th out of 14 countries surveyed (Richards, 2010).

The NHS White Paper *Equity and Excellence: Liberating the NHS* (Department of Health, 2010b) set out the government's ambition for the NHS, stating that:

> **'We want to empower clinicians and to enable them to use the cancer drugs that they and their patients agree are needed to extend or improve life'.**

The Cancer Drugs Fund has thus been established to put clinicians and cancer specialists at the heart of therapeutic decision making, and allow them to use cancer treatments of proven efficacy for their patients' benefit. A Department of Health (2010a) consultation on the Cancer Drugs Fund stated that the fund had been created to cover the costs of clinically-effective cancer drugs, including those that have the following status:

1. Appraised by National Institute of Health and Clinical Excellence but not considered cost effective
2. Licensed and awaiting National Institute of Health and Clinical Excellence appraisal
3. Off-label and where there is sufficient evidence of clinical benefit in individual patients.

The funds are to support treatment for patients who have exhausted the usual individual funding routes of application to primary care trusts providing access to clinically-recommended treatments that are not National Institute of Health and Clinical Excellence approved. Cancer Drugs Fund committees (which are based on strategic health authority boundaries) can also create cohort policies for groups of patients to avoid the bureaucracy of individual funding routes.

In the setting of metastatic colorectal cancer, the Cancer Drugs Fund allows for new applications for funding of treatments such as bevacizumab. In the UK, bevacizumab is approved for use in combination with standard fluoropyrimidine-based chemotherapies for the treatment of metastatic colorectal cancer (Roche Products Ltd, 2011). Data from several clinical trials have demonstrated the clinical benefit of adding bevacizumab to standard chemotherapy in the first-line setting for patients with metastatic colorectal cancer, irrespective of chemotherapy partner (Kabbinavar et al, 2003, 2005; Hurwitz et al, 2004; Saltz et al, 2008; Kozloff et al, 2009; Sobrero et al, 2009). Regimens used include:

- FOLFIRI: folinic acid (leucovorin), 5-fluorouracil and irinotecan
- FOLFOX: folinic acid, 5-fluorouracil and oxaliplatin
- 5-fluorouracil or leucovorin
- Bolus irinotecan-based combination chemotherapy (irinotecan plus fluorouracil or leucovorin)

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- XELIRI: irinotecan and capecitabine
- XELOX: capecitabine plus oxaliplatin.

Despite the available data, many NHS oncologists have only limited experience using bevacizumab in the clinical management of metastatic colorectal cancer. This article provides practical guidance on using bevacizumab appropriately in clinical practice in metastatic colorectal cancer in England. It gives a brief review of the clinical evidence supporting a role for bevacizumab in the treatment of metastatic colorectal cancer, and conveys first-hand experiences of the authors (a group of UK oncologists experienced in using bevacizumab for management of metastatic colorectal cancer) in using this therapeutic agent within metastatic colorectal cancer management. The article reflects the work of a consensus meeting at which the authors reviewed available clinical evidence and current guidelines pertinent to bevacizumab, and agreed a set of summary recommendations for clinical practice in England and optimal use of bevacizumab in metastatic colorectal cancer. It is a companion to a review and practical guide to managing the typical adverse events of bevacizumab across a number of tumour types published in this journal (Miles et al, 2010).

Bevacizumab

Bevacizumab is a humanized monoclonal antibody to vascular endothelial growth factor (VEGF). VEGF is a key driver of vasculogenesis and angiogenesis. Bevacizumab binds VEGF, thus decreasing the free concentration of VEGF able to bind to VEGF receptors. The decreased free concentration of VEGF means there is a lower occupancy of VEGFR-1 and VEGFR-2. Neutralizing the biological activity of VEGF can lead to the regression of the vascularization of tumours, normalization of the remaining tumour vasculature and inhibition of the formation of new tumour vasculature, thereby inhibiting tumour growth and metastasis (Ferrara and Kerbel, 2005; Jain, 2005; Roche Products Ltd, 2011).

Evidence from pivotal randomized controlled trials (*Table 1*), observational studies and post-marketing studies (*Table 2*) in metastatic colorectal cancer show that by adding bevacizumab to chemotherapy, overall survival can be further extended to around 2 years or more in comparison to that observed with chemotherapy alone (Hurwitz et al, 2004, 2009; Saltz et al, 2008; Kozloff et al, 2009; Van Cutsem et al, 2009; Cohn et al, 2010).

Data from several clinical trials have demonstrated the benefit of adding bevacizumab to standard chemotherapy in first-line management of metastatic colorectal cancer (Kabbinavar et al, 2003, 2005; Hurwitz et al, 2004; Saltz et al, 2008; Sobrero et al, 2009). The clinical benefits of combining bevacizumab with chemotherapy have been demonstrated irrespective of whether the chemotherapy partner was irinotecan- or oxaliplatin-based; the efficacy of bevacizumab as first-line treatment for metastatic colorectal cancer with irinotecan-based chemotherapy comes from study AVF2107g (Hurwitz et al, 2004, 2009) and for bevacizumab in combination with oxaliplatin-based chemotherapy from study NO16966 (Saltz et al, 2008). In summary, bevacizumab offers benefits when used with any of the common combination chemotherapy regimens: FOLFIRI, FOLFOX, 5-fluorouracil or leucovorin, bolus irinotecan-based combination chemotherapy, XELIRI or XELOX.

The evidence base for bevacizumab includes three pivotal phase III studies, two conducted in the first-line treatment setting and one in patients previously treated with chemotherapy. The AVF2107g study was a large-scale randomized study in 813 patients with previously untreated metastatic colorectal cancer (*Table 1*) (Hurwitz et al, 2004, 2009). Patients received either bevacizumab 5 mg/kg every 2 weeks in combination with irinotecan-based combination chemotherapy or bolus irinotecan-

Table 1. Pivotal phase III bevacizumab clinical trials in metastatic colorectal cancer

		Progression-free survival				Median overall survival		
Trial	Treatment	Hazard ratio	*P* value	Median (months)	Response rate (%)	Hazard ratio	*P* value	Median (months)
AVF2107g: first line (Hurwitz et al, 2004)	Bevacizumab 5 mg/kg every 2 weeks + IFL (*n*=402)	0.54	<0.001	10.6	45	0.66	<0.001	20.3
	Placebo + IFL (*n*=411)			6.2	35			15.6
E3200: pretreated (Giantonio et al, 2007)	Bevacizumab 10 mg/kg every 2 weeks + FOLFOX4 (*n*=286)	0.61	<0.0001	7.3	23	0.75	*P*=0.0011	12.9
	Bevacizumab 10 mg/kg every 2 weeks (*n*=243)	NR	NR	2.7	3	NR	NR	10.2
	FOLFOX4 (*n*=291)			4.7	9			10.8
NO16966: first line (Saltz et al, 2008)	Bevacizumab 7.5 mg/kg every 3 weeks + XELOX or 5 mg/kg every 2 weeks + FOLFOX4 (*n*=699)	0.83	0.0023	9.4	38	0.89	*P*=0.077	21.3
	Placebo + XELOX/FOLFOX4 (*n*=701)			8.0	38			19.9

FOLFOX4 = oxaliplatin + 5-fluorouracil + leucovorin; IFL = irinotecan + 5-fluorouracil + leucovorin; NR = not reached; XELOX = oxaliplatin + capecitabine.

based combination chemotherapy plus placebo. The primary end point of the study was overall survival. Secondary end points included progression-free survival, response rate, duration of response and safety. Treatment with bevacizumab plus bolus irinotecan-based combination chemotherapy was associated with a median duration of overall survival of 20.3 months compared with 15.6 months in patients given bolus irinotecan-based combination chemotherapy alone (hazard ratio=0.66, $P<0.001$). Addition of bevacizumab to bolus irinotecan-based combination chemotherapy in these patients also significantly increased progression-free survival from 6.2 months to 10.6 months (hazard ratio=0.54, $P<0.001$).

It should be noted that Stathopoulos et al (2010) found that the addition of first-line bevacizumab to bolus irinotecan-based combination chemotherapy in 222 patients with metastatic colorectal cancer did not show any benefit in terms of overall survival or response rate over bolus irinotecan-based combination chemotherapy alone. Progression-free survival, which was not shown in the article, was also reported as showing no benefit. However, this single centre study was statistically underpowered.

A second randomized study in the first-line setting (NO16966) compared bevacizumab in combination with oxaliplatin-based chemotherapy (bevacizumab 5 mg/kg every 2 weeks with FOLFOX4 or bevacizumab 7.5 mg/kg every 3 weeks with XELOX) with XELOX or FOLFOX4 plus placebo in a group of 1401 treatment-naive metastatic colorectal cancer patients (*Table 1*) (Saltz et al, 2008). The primary end point of this study was progression-free survival. Median progression-free survival was 9.4 months in the bevacizumab plus chemotherapy group and 8.0 months in the chemotherapy only group (hazard ratio=0.83, $P=0.0023$). Median overall survival was 21.3 months in the bevacizumab plus chemotherapy group and 19.9 months in the chemotherapy only group (hazard ratio=0.89, $P=0.077$).

A further phase III study in the second-line setting (study E3200) provides evidence of the efficacy of bevacizumab in patients who had received prior chemotherapy but were bevacizumab-naive (Giantonio et al, 2007) (*Table 1*). Patients ($n=829$) with metastatic colorectal cancer were randomly assigned to one of three treatment groups: bevacizumab 10 mg/kg every 2 weeks in combination with FOLFOX4, bevacizumab 10 mg/kg every 2 weeks alone, or FOLFOX4 alone. The primary end point was overall survival. The overall survival in patients treated with bevacizumab plus FOLFOX4 was 12.9 months compared with 10.8 months for FOLFOX4 alone (hazard ratio=0.75, $P=0.0011$) and 10.2 months for bevacizumab alone (*Table 1*).

Additional supportive data on the efficacy of the combination of bevacizumab and chemotherapy as treatment for metastatic colorectal cancer come from 'real-world' pragmatic phase IV studies such as First BEAT – a fully monitored, prospective study (Van Cutsem et al, 2009), BRiTE (Grothey et al, 2008; Kozloff et al, 2009) and from a large, community-based, observational German registry study (Arnold et al, 2011) (*Table 2*). In First BEAT, treatment with bevacizumab plus chemotherapy partners FOLFIRI, FOLFOX and XELOX was associated with median progression-free survival and median overall survival values similar to those observed in randomized controlled studies (*Tables 1* and *2*), with overall survival extended beyond 22 months. In BRiTE, the overall survival for all bevacizumab plus chemotherapy regimens was 25.1 months. In the German registry, all bevacizumab plus chemotherapy regimens were associated with a progression-free survival of 10.2 months, and with an overall survival of 25.5 months.

The phase II BOXER and GONO studies offer data on bevacizumab in patients with metastatic colorectal cancer and liver metastases (Masi et al, 2010; Wong et al, 2011). The GONO trial involved 57 patients with unresectable liver metastases, induction treatment included bevacizumab (5 mg/kg) plus FOLFOXIRI (5-fluorour-

Table 2. Bevacizumab in combination with chemotherapy for metastatic colorectal cancer in real-world studies*

Study	Patients	Treatment	Median progression-free survival (months)	Median overall survival (months)
First BEAT (Van Cutsem et al, 2009)	1914	All treatments	10.8	22.7
		Bevacizumab + FOLFIRI	11.6	23.7
		Bevacizumab + FOLFOX	11.3	25.9
		Bevacizumab + XELOX	10.8	23.0
		Bevacizumab + monotherapy fluoropyrimidine	8.6	18.0
BRiTE (Grothey et al, 2008; Kozloff et al, 2009)	1953	All bevacizumab + chemotherapy regimens	10.0	25.1 †
German community-based observational cohort (Arnold et al, 2011)	1620	All bevacizumab + chemotherapy regimens	10.2	25.5

* Choice of chemotherapy was at the physician's discretion; † overall survival increased to 31.8 months when patients treated beyond progression of disease. FOLFIRI = leucovorin + 5-fluorouracil + irinotecan; FOLFOX = oxaliplatin + 5-fluorouracil + leucovorin; XELOX = oxaliplatin + capecitabine.

acil, oxaliplatin and irinotecan combined) for 6 months, followed by bevacizumab maintenance treatment. The progression-free survival at 10 months was 74% (Masi et al, 2010). The BOXER study involved 46 patients with unresectable colorectal liver metastases and sought to determine a neoadjuvant role for bevacizumab in combination with chemotherapy. Patients received perioperative XELOX (capecitabine and oxaliplatin) plus bevacizumab. Treatment with bevacizumab plus chemotherapy resulted in an objective response rate of 76% such that 40% of patients became suitable for resection (Wong et al, 2011).

Anti-epidermal growth factor receptor antibodies cannot inhibit signalling through epidermal growth factor receptor in the presence of Kras mutations. This is because mutations in Kras lead it to be constituently active and thus independent of epidermal growth factor receptor signalling. Around 40% of colorectal cancers have mutant Kras, and it is widely accepted that these patients should not receive anti-epidermal growth factor receptor antibodies at any stage of their treatment (Monzon et al, 2009). An important and distinguishing feature of bevacizumab as a biological therapy for use in combination with chemotherapy in metastatic colorectal cancer is that this targeted agent has proven to be efficacious in treating metastatic colorectal cancer irrespective of known Kras mutational status (Hurwitz et al, 2009; Tol et al, 2009).

Current clinical guidelines on metastatic colorectal cancer: role for bevacizumab

It is recommended that UK physicians follow National Institute of Health and Clinical Excellence guidance; however, the Cancer Drugs Fund has given the opportunity for clinicians to access cancer drugs previously not recommended by National Institute of Health and Clinical Excellence. In the absence of UK-specific guidelines oncologists can also refer to a number of clinical practice guidelines which also capture the available evidence base and offer recommendations on the management of patients with metastatic colorectal cancer. These include those from the European Society of Medical Oncology (Van Cutsem et al, 2010) and the US National Comprehensive Cancer Network (Engstrom et al, 2011), both of which support the use of bevacizumab in combination with chemotherapy as first-line treatment for metastatic colorectal cancer.

UK experience and recommendations regarding use of bevacizumab in metastatic colorectal cancer

The authors have extensive first-hand experience of using bevacizumab plus chemotherapy in the management of patients with metastatic colorectal cancer. As a general principle, physicians in England should follow accepted clinical guideline recommendations such as those of European Society of Medical Oncology and National Comprehensive Cancer Network that support a first-line role for bevacizumab in metastatic colorectal cancer (Van Cutsem et al, 2010; Engstrom et al, 2011).

Based on evidence, guidelines and clinical experience, the authors recommend that bevacizumab-based therapy should be considered as first-line treatment for metastatic colorectal cancer in patients with newly diagnosed metastatic disease and also in those whose disease has progressed after receiving first-line chemotherapy (Hurwitz et al, 2004; Giantonio et al, 2007; Saltz et al, 2008; Roche Products Ltd, 2011). All fluoropyrimidine-based chemotherapy partners should be considered, depending on physician and patient preferences and on patient profile.

An important practical point is that bevacizumab is given as a short infusion intravenously over 30 minutes. There are very few infusional reactions which require the infusion to be stopped or slowed. Thus the impact on delivery of chemotherapy is minimal.

Treatment with bevacizumab until disease progression is the recommended approach that derives the greatest patient benefit and it is important not to stop bevacizumab therapy in patients requiring modifications to chemotherapy before disease progression (Saltz et al, 2008; Roche Products Ltd, 2011).

The more frequent adverse events associated with bevacizumab tend to be mild or moderate in severity, and are largely manageable. Physicians are referred to the consensus review by Miles et al (2010) for comprehensive guidance on how to anticipate and manage any bevacizumab-related treatment adverse events.

All comorbidities should be considered in terms of risk/benefit to the patient and it is wise to exercise caution in those patients who have the comorbidities identified in *Table 3*.

There may be a need for caution in certain patient groups – such as those patients with colonic stents (who may be at an increased risk of perforation), those patients with tumours at imminent risk of obstruction or perforation and patients with inflammatory bowel disease.

There is no requirement for Kras mutational status testing when using bevacizumab.

Table 3 summarizes the author group recommendations and *Figure 1* summarizes the bevacizumab–chemotherapy combinations that may be used in first-line management of metastatic colorectal cancer.

Conclusions

The advent of the Cancer Drugs Fund provides the opportunity for more patients in England access to bevacizumab therapy for metastatic colorectal cancer. There is a strong evidence base supporting use of bevacizumab plus chemotherapy to improve progression-free survival and overall survival in metastatic colorectal cancer. Current European Society of Medical Oncology and National Comprehensive Cancer Network guidelines recommend first-line use of bevacizumab with all major

chemotherapy partners in metastatic colorectal cancer. The authors consider that the practical recommendations outlined in this article integrate the evidence base, current guidance and their practical experiences to provide physicians in England with practical guidance on using first-line bevacizumab-based therapy in the management of patients with metastatic colorectal cancer. **BJHM**

Conflict of interest: None of the panel was paid to attend the meeting relating to the development of these practical recommendations. Roche Products Limited sponsored the meeting and funded medical writing support for the development of the manuscript. Dr S Raouf has received honoraria from Roche and Pierre Fabre; Dr J Bridgewater has received honoraria from Roche for attendance at advisory boards; Dr R Ellis has received honoraria from Roche and Merck Serono; Professor D Ferry has received honoraria in an advisory capacity from Roche, Lilly, AstraZeneca, Novartis, Bayer, Sanofi Aventis, Boehringer Ingelheim and MSD and has received research funding from AZ and Lilly; Dr M Hill has received sponsorship from Roche to attend international oncology congresses and honoraria for advisory boards and Dr H Wasan has been a consultant in an advisory role and spoken at meetings over the last 3 years by Roche, Merck, Merck KgA, Amgen, Pfizer, Novartis, Bayer, Sanofi-Aventis bioTheranostics, Pasteur-bioMerieux and Sirtex Medical.

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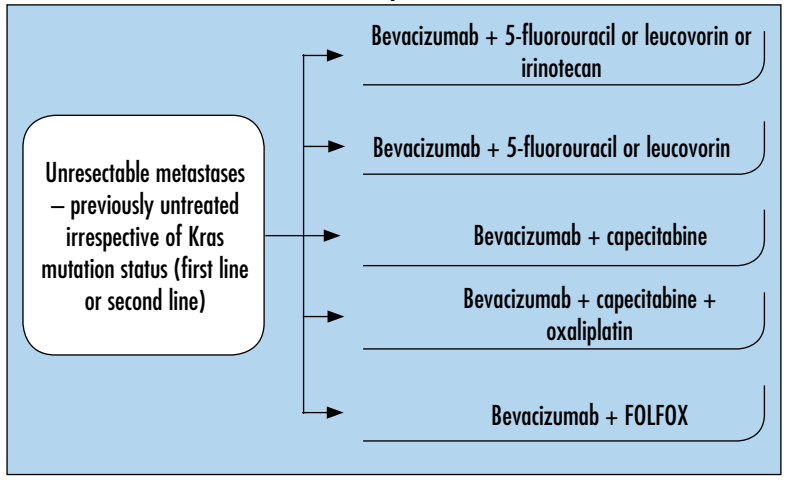
Table 3. UK expert recommendations on use of bevacizumab in metastatic colorectal cancer

Treatment line and chemotherapy partners	Bevacizumab-based therapy should be considered as first-line treatment for metastatic colorectal cancer in patients with newly diagnosed metastatic disease and in those whose disease has progressed after receiving chemotherapy for early stage disease
	Bevacizumab could be considered as second-line treatment for metastatic colorectal cancer in bevacizumab-naive patients
	All fluoropyrimidine-based chemotherapy partners can be considered for use with bevacizumab, with choice of regimen depending on physician and patient preferences
	It is recommended that treatment with bevacizumab until disease progression derives the greatest patient benefit and it is important not to stop bevacizumab in patients requiring modifications to chemotherapy before disease progression (Saltz et al, 2008; Roche Products Ltd, 2011)
Patient selection	Consider bevacizumab-based therapy for all eligible patients, including performance status 0–2, in combination with an appropriate chemotherapy partner
	Consider bevacizumab-based therapy for elderly patients aged over 65 years, providing they have good performance status and after exclusion of comorbidities
Comorbidities	The most frequent adverse events associated with bevacizumab tend to be mild or moderate in severity, and are largely predictable and manageable
	All comorbidities should be considered in terms of risk/benefit to the patient and it is wise to exercise caution in patients who have the following comorbidities: history of cardiovascular disease (ischaemic heart disease, acute myocardial infarction), cerebrovascular disease (prior transient ischaemic attack or cerebrovascular accident), recent cardiac event, venous thromboembolism and delay in wound healing or wound healing complications

Figure 1. UK expert recommendations on the use of bevacizumab for the treatment of metastatic colorectal cancer. FOLFOX = oxaliplatin + 5-fluorouracil + leucovorin.



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KEY POINTS

- The Cancer Drugs Fund potentially allows more patients in England access to clinically effective cancer therapies including bevacizumab for patients with metastatic colorectal cancer.
- This review contains a brief outline of the clinical evidence supporting a role for bevacizumab in the treatment of metastatic colorectal cancer and offers guidance based on first-hand experience in using this therapeutic agent within metastatic colorectal cancer management.
- Bevacizumab-based therapy should be considered as first-line treatment for metastatic colorectal cancer in patients with newly diagnosed metastatic disease and in those whose disease has progressed after receiving prior chemotherapy for metastatic disease.

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