Executive Summary

Context

Bevacizumab (Avastin) is a humanized (93% human) murine monoclonal antibody which binds to and neutralizes VEGF, a powerful pro-angiogenic glycoprotein produced by both normal and neoplastic cells, first isolated by Ferrara and Henzel in 1989. VEGF encourages nearby blood vessels to sprout and provide a vascular supply to the developing tumour. Depriving tumours of VEGF has several effects that are relevant to the therapeutic use of bevacizumab. These include preventing the development of new tumour blood vessels, causing the regression of existing vasculature and normalizing the function of the remaining tumour blood vessels resulting in enhanced delivery of concomitantly administered cytotoxic drugs (Klement, G et al. 2000).

Bevacizumab is currently licensed for the following indication relevant for this NICE review:

"… in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum." (Bevacizumab SmPC, 2010)

The original marketing authorisation for bevacizumab in metastatic colorectal cancer, restricted it to use in the first-line setting in combination with 5-FU-based chemotherapy with or without irinotecan, based on the Phase III trial data then available (Bevacizumab SmPC, 2010; Hurwitz, H et al, 2004). With the availability of further studies showing that bevacizumab added to combinations of 5-fluorouracil or capecitabine and oxaliplatin in the first- or second-line settings also improved treatment outcomes, the EMEA took the pragmatic view that the benefits of bevacizumab in metastatic colorectal cancer were dependent on neither the specific nature of the chemotherapy with which it was used nor the line of treatment.

Consequently they granted the broad Marketing Authorisation detailed above, even though not all bevacizumab-chemotherapy combinations at all treatment lines have been tested in large clinical trials. In particular, the EMEA did not consider that a second-line study comparing chemotherapies other than those containing oxaliplatin with or without bevacizumab was required and as such a study has not been conducted.

The scope of this appraisal covers the use of bevacizumab in combination with non-oxaliplatin-based chemotherapy for the treatment metastatic colorectal cancer after disease progression on first line treatment. The use of fluoropyrimidines is well established as the backbone of chemotherapy regimens for treating this disease, in combination with other agents such as oxaliplatin and irinotecan (Terstriep et al, 2006).

In the UK, for patients fit enough for combination chemotherapy, the most widely use *first-line* treatment for metastatic colorectal cancer (mCRC) is a combination of oxaliplatin and 5-FU, whilst irinotecan (usually in combination with 5-FU) is the predominant second-line treatment. Therefore in this appraisal the most pertinent questions in relation to bevacizumab are 'what benefit does bevacizumab confer when added to standard irinotecan-based second line therapy?' and 'is the extent of this benefit sufficient to warrant the incremental expenditure required to fund bevacizumab in this setting?'.

As shown in Table 1, the addition of bevacizumab to combination chemotherapy regimens has demonstrated improved outcomes in previously untreated metastatic colorectal cancer patients when added to irinotecan, oxaliplatin or fluoropyrimadine-based chemotherapy and also in relapsed patients treated with oxaliplatin-based chemotherapy. However (as demonstrated in the below matrix) there is no randomised evidence on the use of bevacizumab in combination with non-oxaliplatin based chemotherapy following disease progression on first line treatment.

This 'evidence gap' is in part a product of (1) the divide between the requirements of a regulatory body such as the EMA and those of a reimbursement body such as NICE, (2) the ethical difficulty in conducting a study in a setting in which patients may be randomised to a non-biologic containing control arm (which the totality of evidence available suggests would be significantly inferior) and (3) the divide between clinical practice in the UK and the rest of the world.

Table 1: The randomized evidence base for bevacizumab in mCRC

Line of Treatment	Oxaliplatin Based	Irinotecan Based	5-FU/FA
1st Line	966 Study PFS HR = 0.83 OS HR = 0.89	Hurwitz 2004 PFS HR = 0.54 OS HR = 0.66	Kabbinavar 2005 PFS HR = 0.50 OS HR = 0.79
2nd Line	E3200 Study PFS HR = 0.61 OS HR = 0.75	No RCT Evidence (Setting of this appraisal)	No RCT Evidence (Setting of this appraisal)

The evidence highlighted above indicates it is reasonable to expect that bevacizumab will also improve outcomes in relapsed patients treated with irinotecan-based chemotherapy. This logic was applied by the EMA in granting a marketing authorisation that includes this situation, despite the lack of Phase 3 RCT evidence in this specific setting.

Whilst there are no RCTs comparing bevacizumab with a fluoropyrimidine +/- irinotecan in the second-line setting the randomized evidence available in other settings supported by the additional data from observational studies and smaller and early phase studies (summary of available evidence provided in Tables 1 and 2), indicate that bevacizumab is safe and effective in combination with irinotecan in 2nd line mCRC. However quantifying the magnitude of efficacy gained from adding bevacizumab to FOLFIRI (the most commonly utilized irinotecan based regimen in 2nd line) is difficult.

Without biologic therapy median PFS for FOLFIRI based therapy in 2nd line is approximately 2.5 months (Tournigand, 2004) whilst naive indirect comparison with the limited data available suggests that given treatment with B-FOLFIRI this may rise to somewhere between 4 and 10 months (Bekaii-Saab TS et al. 2010, Bennouna J et al. 2009, Yidiz R et al 2010 – see appendix 2).

Table 2: Summary of OS, PFS and RR across studies evaluating the use of bevacizumab in the treatment of metastatic colorectal cancer in 1st and 2nd line settings

Study	**Intervention**	**Population**	**Comparator**	**Intervention**			**More details can be found in section:**
				OS (months)	**PFS (months)**	**RR (%)**	
Hurwitz, H. et al. (2004) n = 813	bevacizumab plus irinotecan, bolus fluorouracil, and leucovorin (IFL)	previously untreated patients with metastatic colorectal cancer	irinotecan, bolus fluorouracil, and leucovorin (IFL) plus placebo	20.3*	10.6*	44.8*	1.1.1
Kabbinavar, F. et al. (2005) n = 209	bevacizumab plus bolus fluorouracil, and leucovorin (FU/LV)	previously untreated patients with metastatic colorectal cancer	bolus fluorouracil, and leucovorin (FU/LV)	16.6	9.2*	26	1.1.2
Saltz, L. et al. (2008) n = 1401	bevacizumab plus oxaliplatin-based chemotherapy (FOLFOX or XELOX)	previously untreated patients with metastatic colorectal cancer	oxaliplatin-based chemotherapy (FOLFOX or XELOX)	21.3	9.4*	Not reported	1.1.3
Giantonio, B. et al. (2007) n = 829	bevacizumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4)	previously treated patients with metastatic colorectal cancer	oxaliplatin-based chemotherapy (FOLFOX4)	12.9*	7.3*	22.7*	1.2.1
Grothey, A. et al. (2008) n = 1445	bevacizumab as 2nd line treatment ("Bevacizumab beyond first progression") after progression of the disease	patients with metastatic colorectal cancer treated, previously untreated or treated with bevacizumab as 1st line treatment	no treatment after progression of the disease ("no post-progression of disease (PD))" treatment, systemic therapy post-progression of disease but without bevacizumab ("Post-PD treatment without bevacizumab")	31.8*	19.2*	Not reported	A2.1
Bekaii-Saab TS et al. (2010) n = 489	bevacizumab plus chemotherapy (bevacizumab-	metastatic colorectal cancer patients receiving 1st or 2nd	non-bevacizumab-based (bevacizumab-naive)	17.5	8.0	Not reported	A2.2

	exposed)	line treatment	chemotherapy regimen				
Degirmenci−M et al. (2010) n = 53	bevacizumab plus capecitabine and irinotecan regimen	metastatic colorectal cancer patients receiving 1st line; or 2nd line or later	bevacizumab plus capecitabine and irinotecan regimen given	15.2 (2^{nd} line or later)	10.2 (2^{nd} line or later)	Not reported for 2^{nd} line or later	A2.3
Lièvre, A. et al. (2009) n = 31	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer (the number of patients receiving only 2nd line treatment with bevacizumab plus irinotecan-based chemotherapy is not specified)	bevacizumab plus oxaliplatin-based chemotherapy	18.4 (2^{nd} or 3^{rd} line)	9.7 (2^{nd} or 3^{rd} line)	45.4*	A2.4
Senellart H et al. (2008); Bennouna J et al. (2009) n = 53	bevacizumab plus chemotherapy	previously treated patients with metastatic colorectal cancer	n/a	21.7(with FOLFIRI); 24.1 (with irinotecan);14.5 (with XELIRI)	7.8(with FOLFIRI); 8.4 (with irinotecan); 2.6 (with XELIRI)	11.0 (with FOLFIRI); 2.0 (with irinotecan); 0 (with XELIRI)	A2.5
Yildiz, R. et al. (2010) n = 40	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer (the number of patients receiving only 2nd line treatment with bevacizumab plus irinotecan-based chemotherapy is not specified)	n/a	14.0	6.0	20.0	A2.6
Akiyoshi, K. et al. (2010) n = 25	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer (the number of patients receiving only 2nd line treatment with bevacizumab plus	n/a	Not reported	9.7	24.0	A2.7

		irinotecan-based chemotherapy is not specified)					
Kang−Byung−Woog et al. (2009) n = 42	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer	bevacizumab plus oxaliplatin-based chemotherapy	9.5 (no breakdown for irinotecan-based therapy only)	5.3 (no breakdown for irinotecan-based therapy only)	9.5 (no break-down for irinotecan-based therapy only)	A2.8
Kwon−Hyuk−Chan et al. (2007) n = 14	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer	n/a	10.9	3.9	28.5	A2.9
Popov, I. et al. (2007) n = 30	bevacizumab as 2nd line or later therapy plus chemotherapy	previously treated patients with metastatic colorectal cancer	bevacizumab as 1st line therapy plus chemotherapy	7.0	5.5	14.0	A2.10
Samelis, GF. et al. (2007) n = 32	bevacizumab plus irinotecan-based chemotherapy	previously treated patients with metastatic colorectal cancer	n/a	12.0	8.0	37.5	A2.11
Vincenzi, B et al. (2009) n = 48	bevacizumab plus fluoropyrimidine-based chemotherapy only	previously treated patients with metastatic colorectal cancer	n/a	7.7	3.5	6.5	A2.12
Chen H et al. (2006) n = 350	bevacizumab plus fluoropyrimidine-based chemotherapy only	previously treated patients with metastatic colorectal cancer	n/a	9.0	3.5	4.0 (investi-gator review); 1.0 (independ-ent review)	A2.13
* = P<0.05							

Note: Section A2 refers to appendix 2

In order to aid the Committee in their determinations, the data available for bevacizumab in combination with irinotecan as a first line treatment for mCRC are presented within this document. In addition details of the small controlled and uncontrolled studies that evaluated the use of bevacizumab are detailed and described in order to support the assertion that, whilst it is difficult to quantify the precise magnitude of benefit offered by bevacizumab in this setting, the totality of the evidence available suggests that bevacizumab in combination with FOLFIRI (B-FOLFIRI) is safe and efficacious in 2nd line mCRC.

Evidence on the efficacy of bevacizumab in K-ras wild type patients

The scope for this submission covers novel treatments for which K-ras mutation status appears to be a significant negative prognostic indicator for the successful outcome of treatment. Although K-ras is involved in the EGFR signaling pathway which mediates the action of cetuximab and panitumumab and K-ras mutations determine sensitivity to these drugs, signalling in the VEGF receptor pathway which mediates the action of bevacizumab, does not involve K-ras. Therefore, as expected, studies have shown that bevacizumab is clinically effective, regardless of K-ras status, avoiding the need for testing and possible delays to treatment (Hurwitz et al. 2009).

Evidence on the relative efficacy of bevacizumab, cetuximab and panitumumab

There are, as yet, no published direct comparisons of the safety, efficacy and tolerability of bevacizumab, cetuximab and panitumumab. Due to the lack of randomised evidence on the use of bevacizumab in combination with non-oxaliplatin based chemotherapy after disease progression on first line therapy it is not possible to make a formal indirect comparison of bevacizumab to the other two biologics under assessment.

The cost effectiveness of bevacizumab

As noted above, whilst there is good evidence suggesting that bevacizumab in combination with non-oxaliplatin based chemotherapy beyond first line would offer meaningful clinical benefit the absence of randomized evidence in this setting makes the quantification of the extent of that benefit, and the estimated ICER derived via that quantification, subject to sizeable uncertainty.

Given the paucity of randomised evidence relevant to this appraisal we provide a qualitative assessment of the cost-effectiveness of bevacizumab supported by some quantitative elements rather than presenting a formal cost-effectiveness analysis. Without pursuing a route of formal cost-effectiveness analysis it is clear from the indicated regimens for each treatment and the purchase prices of each technology that bevacizumab based regimens are likely considerably cheaper than both cetuximab and panitumumab based regimens.

<u>The cost effectiveness of B-FOLFIRI vs FOLFIRI (the standard of care in this line of treatment)</u>

The evidence required to conduct this analysis is not available.

Whilst exploratory analyses may be conducted in order to investigate what the cost-effectiveness of bevacizumab in this setting may be given certain assumed PFS and OS HRs and the utilisation of non-biologic irinotecan based PFS and OS baseline risk curves (such as those available in Tournigand et al, 2004) these would be subject to sizeable uncertainty.

<u>The cost effectiveness of B-FOLFIRI vs C-FOLFIRI (Cetuximab in combination with FOLFIRi)</u>

Whilst there is sizeable uncertainty as to the relative efficacy of bevacizumab based regimens and non-bevacizumab based regimens under assessment in this appraisal in the setting of interest (2nd and later lines of treatment) it is clear that B-FOLFIRI (bevacizumab in combination with the FOLFIRI regimen) would offer significant cost-advantages in 2nd line when compared to C-FOLFIRI (cetuximab in combination with FOLFIRI).

Cetuximab has a considerably higher drug cost per cycle than bevacizumab, requires additional diagnostic testing and requires an additional hospital based administration every cycle of C-FOLFIRI beyond that required for B-FOLFIRI or FOLFIRI alone. In total a 7 cycle course of C-FOLFIRI for an

average 75 kg 1.75 m^2 BSA patient is £5,408 more expensive than an equivalent course of B-FOLFIRI.

Table 3: C-FOLFIRI vs B-FOLFIRI incremental cost over a 7 cycle course of treatment

	Incremental Cost (C-FOLFIRI vs B-FOLFIRI)
KRAS testing	£462
Drug Costs	£3,357
Administration Costs	£1,589
Total Costs	£5,408

In order to be considered cost-effective against B-FOLFIRI at a cost effectiveness threshold of £30,000/QALY C-FOLFIRI would have to produce an additional 0.18 QALYs above those provided by B-FOLFIRI. At an assumed utility value of 0.6 (ScHARR TA118 PD Utility) this would require C-FOLFIRI to have a 3.6 month overall survival advantage over B-FOLFIRI which appears unlikely given the evidence currently available on the efficacy of Cetuximab in this setting.

As panitumumab is currently only indicated as a monotherapy for use in third line it is extremely difficult to make any meaningful comparison of bevacizumab and panitumumab.

Conclusion

Data supporting the use of bevacizumab beyond first line treatment of metastatic colorectal carcinoma with non-oxaliplatin-based chemotherapy does not currently comprise of any large randomised controlled trials. Some evidence exists in the form of observational study data and some data from small controlled studies (randomised and non-randomised).

However there is substantial evidence showing the safety, efficacy and tolerability of bevacizumab in metastatic colorectal carcinoma for first line use with several chemotherapy regimens and in second line use with oxaliplatin-based chemotherapies. In addition, there are data from the control groups of randomised clinical trials with other biologic agents which appear to reinforce the safety, efficacy and tolerability of bevacizumab in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum.

From this it is possible to predict qualitatively the safety, efficacy and tolerability of bevacizumab in combination with chemotherapy other than oxaliplatin beyond first line use, but the explicit and formal quantification of the extent of this efficacy for the purposes of a cost-utility analysis would be subject to a great deal of uncertainty.

What is clear is that B-FOLFIRI is considerably less costly than C-FOLFIRI and that despite the uncertainty surrounding the efficacy of B-FOLFIRI in second line it would appear extremely unlikely that C-FOLFIRI would be associated with the efficacy gain required to be considered a cost-effective use of NHS resources.