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The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales

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ABSTRACT

Background: Bevacizumab is a humanised monoclonal antibody, which has demonstrated significant activity in metastatic colorectal cancer. The aim of this study is to estimate the cost-effectiveness of adding bevacizumab to chemotherapy for patients with untreated metastatic colorectal cancer.

Methods: A decision-analytic model was developed to estimate the lifetime costs and benefits of adding bevacizumab to irinotecan plus FU/LV (IFL) or 5-FU/LV alone. Effectiveness outcomes, health utilities and resource use data were derived from recent bevacizumab RCTs and from the literature.

Results: Adding bevacizumab to IFL costs approximately £62,857 per QALY gained. Adding bevacizumab to 5-FU/LV costs approximately £88,436 per QALY gained. The acquisition cost of bevacizumab is a key determinant of its cost-effectiveness. The probability that bevacizumab has a cost-effectiveness ratio that is better than £30,000 per QALY gained is close to zero.

Conclusions: Given high acquisition costs in relation to clinical benefits, bevacizumab is unlikely to represent a cost-effective use of NHS resources.

1. Introduction

Colorectal cancer is the third most commonly diagnosed cancer in England and Wales, with over 30,600 new cases registered in England and Wales in 2003.[1] For approximately 14,000 cases in England and Wales, colorectal cancer is registered as the underlying cause of death each year.[1] The onset of metastatic disease is associated with poor outcomes for the vast majority of patients. For these patients, cytotoxic therapy represents the cornerstone of treatment. The armoury of options for the treatment of colorectal cancer is constantly evolving, and clinical evidence suggests that newer agents for the treatment of metastatic disease may confer survival benefits as well as symptom control and palliation. Oxaliplatin and irinotecan are now well established as clinically effective and cost-effective treatment options for metastatic disease in England and Wales.[2] More recently, clinical research and development has focussed on evaluating the efficacy of the monoclonal antibodies, which are thought to selectively target receptors in the body which cause cancer.

As new treatments become available, there is a need to consider not only whether they are effective in clinical practice, but also whether they represent a valuable use of resources for the healthcare service, that is, whether they are cost-effective in comparison to current standard therapies. The aim of this study is to estimate the expected costs and health outcomes resulting from the use of bevacizumab plus chemotherapy in comparison to chemotherapy alone in the treatment of metastatic colorectal cancer. This study was commissioned by the NHS HTA Programme to inform the

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National Institute for Health and Clinical Excellence's (NICE) Technology Appraisal of bevacizumab in the treatment of metastatic colorectal cancer in England and Wales.

2. Materials and methods

2.1. Model scope

We developed a health economic model to estimate the marginal cost-effectiveness of two bevacizumab-containing chemotherapy regimens for the first-line treatment of metastatic colorectal cancer. The first comparison estimates the marginal cost-effectiveness of first-line bevacizumab in combination with irinotecan and 5-FU/LV as compared to irinotecan and 5-FU/LV. The second comparison estimates the marginal cost-effectiveness of first-line bevacizumab in combination with 5-FU/LV as compared to 5-FU/LV alone. Table 1 describes the treatment regimens evaluated within the decision-analytic model.

A simplified schematic of the decision-analytic model is presented in Fig. 1. The model assumes that costs and health-related quality of life are primarily dependent on the presence or absence of disease progression. The model assumes three states of health: alive without disease progression; alive following disease progression; and dead. Patients enter the model at the point at which they would be considered eligible for treatment with bevacizumab (in the alive progression-free health state) and receive one of the active therapy regimens until they subsequently experience disease progression, intolerable adverse events and/or death. In the event of documented disease progression, the model assumes that patients enter the post-progression state, whereby a proportion of patients are assumed to receive oxaliplatin plus 5-FU/LV as second-line treatment, and a smaller proportion of

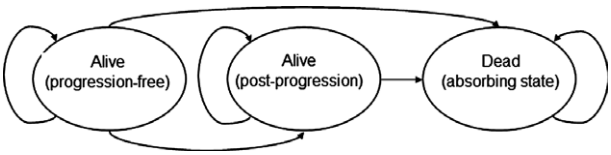

Fig. 1 – Model schematic.

Table 1 – Treatment regimens included in the health economic model

Chemotherapy regimen	5-FU regimen	Cycle duration	Line of treatment	Chemotherapy regimen components and protocol dose
Bevacizumab plus irinotecan plus FU/LV (IFL)	Roswell Park (bolus)	6 weeks	First-line	*Weekly for 4 weeks, then 2 weeks rest (4 doses per cycle)* 125 mg/m^2 irinotecan 500 mg/m^2 5-FU 20 mg/m^2 leucovorin *Once every two weeks (3 doses per cycle)* 5 mg/kg bevacizumab
Bevacizumab plus 5-FU/LV	Roswell Park (bolus)	8 weeks	First-line	*Weekly for 6 weeks, then 2 weeks rest (6 doses per cycle)* 500 mg/m^2 5-FU 500 mg/m^2 leucovorin *Once every two weeks (4 doses per cycle)* 5 mg/kg bevacizumab
IFL	Roswell Park (bolus)	6 weeks	First-line	*Weekly for 4 weeks, then 2 weeks rest (4 doses per cycle)* 125 mg/m^2 irinotecan 500 mg/m^2 5-FU 20 mg/m^2 leucovorin
5-FU/LV	Roswell Park (bolus)	8 weeks	First-line	*Weekly for 6 weeks, then 2 weeks rest (6 doses per cycle)* 500 mg/m^2 5-FU 500 mg/m^2 leucovorin
Oxaliplatin plus 5-FU/LV	Modified de Gramont (infusional)	2 weeks	Second-line	*Once every 2 weeks* 175 mg folinic acid 400 mg/m^2 5-FU 2800 mg/m^2 5-FU 85 mg/m^2 oxaliplatin
Mitomycin-C plus 5-FU	Protracted venous 5-FU	6 weeks	Third-line	*Once every 6 weeks* 7 mg/m^2 mitomycin *Daily* 300 mg/m^2/24 h 5-FU

patients subsequently receive Mitomycin-C plus protracted 5-FU/LV as third-line treatment. Following active treatment, patients are assumed to receive best supportive care until death. Survival modelling techniques were used to estimate the expected progression-free survival and overall survival durations for patients with previously untreated metastatic colorectal cancer who receive bevacizumab plus chemotherapy or chemotherapy alone. The survival models were then used to estimate expected life years, QALYs gained and costs for each treatment group.

2.2. Systematic review of clinical effectiveness

We undertook a systematic review to identify all comparative randomised controlled trials (RCTs) relating to the clinical effectiveness of bevacizumab in combination with chemotherapy in comparison to chemotherapy alone in patients with previously untreated metastatic colorectal cancer.[3] The systematic searches identified three RCTs, which were included in the systematic review of clinical effectiveness. Study AVF2107g was a large Phase III RCT, which compared bevacizumab plus IFL (irinotecan plus FU/LV) against IFL alone.[4] The remaining two trials AVF2192g and AVF0780g were smaller Phase II RCTs, which compared bevacizumab plus FU/LV against FU/LV alone.[5,6] Overall survival was specified as the primary end-point within two of the studies,[4,5] whilst study AVF0780g used time to disease progression and tumour response rate as the primary end-points.[7] Further details of the systematic review methods are available from the full study report.[3] The key results of the systematic review are presented in Table 2. None of the studies reported the impact of bevacizumab upon health-related quality of life. Owing to considerable heterogeneities in terms of patient populations and the treatments within studies AVF2107g and AVF2192g, marginal rather than incremental cost-effectiveness estimates are presented.

2.3. Survival modelling methods

Kaplan–Meier curves giving empirical estimates of progression-free survival and overall survival in each of the four treatment groups were obtained from the trial publications for studies AVF2107g and AVF2192g.[4,5] Study AVF0780g was not used within the model as it was not powered to demonstrate the impact of treatment on overall survival. As some patients were still alive at the end of studies AVF2107g and AVF2192g,[4,5] the final portion of each survival curve was extrapolated using regression analysis to estimate the parameters of a Weibull survival curve. Independent models were constructed to describe the probability of overall survival and progression-free survival over time within each of the four treatment groups, based on Collett's formulation of the Weibull distribution.[7]

Table 2 – Systematic review results on the clinical effectiveness of bevacizumab

Study	Treatment group	Median OS (months)	Hazard ratio (intervention versus comparator)	Significance
Overall survival outcomes				
Hurwitz et al.[4]	IFL + BV (5 mg/kg)	20.3	0.66	$p < 0.001$
Study AVF2107g	IFL	15.6	–	
Kabbinavar et al.[6]	FU/LV + BV (5 mg/kg)	21.5	0.63	Not reported
Study AVF0780g	FU/LV + BV (10 mg/kg)	16.1	1.17	Not reported
	FU/LV	13.8	–	
Kabbinavar et al.[5]	FU/LV + BV (5 mg/kg)	16.6	0.79	$p = 0.16$
Study AVF2192g	FU/LV	12.9	–	
Study	Treatment group	Median PFS (months)	Hazard ratio (intervention versus comparator)	Significance
Progression-free survival outcomes				
Hurwitz et al.[4]	IFL + BV (5 mg/kg)	10.6	0.54	$p < 0.001$
Study AVF2107g	IFL	6.2	–	
Kabbinavar et al.[6]	FU/LV + BV (5 mg/kg)	–	–	–
Study AVF0780g	FU/LV + BV (10 mg/kg)	–	–	–
	FU/LV	–	–	
Kabbinavar et al.[5]	FU/LV + BV (5 mg/kg)	9.2	0.50	$p = 0.0002$
Study AVF2192g	FU/LV	5.5	–	
Study	Treatment group	Tumour response rate (%)	Difference (intervention versus control)	Significance
Overall tumour response rates				
Hurwitz et al.[4]	IFL + BV (5 mg/kg)	44.8	+10.0	$p = 0.004$
Study AVF2107g	IFL	34.8	–	
Kabbinavar et al.[6]	FU/LV + BV (5 mg/kg)	40	+23	$p = 0.029$
Study AVF0780g	FU/LV + BV (10 mg/kg)	24	+7	$p = 0.434$
	FU/LV	17	–	
Kabbinavar et al.[5]	FU/LV + BV (5 mg/kg)	26.0	+10.8	$P = 0.055$
Study AVF2192g	FU/LV	15.2	–	

BV, bevacizumab.

The area under each curve was calculated to provide an estimate of the mean duration of time spent alive and the mean duration of time spent without disease progression. The difference between the mean overall survival duration and the progression-free survival duration was used to provide a direct estimate of the mean survival duration following disease progression for each treatment group.

2.4. Modelling health-related quality of life

One of the principal aims of treatment for patients with metastatic colorectal cancer is to slow disease progression, hence controlling symptoms of the disease. However, the systematic review of clinical effectiveness did not identify any evidence concerning the impact of bevacizumab on health-related quality of life using preference-based instruments which could enable the calculation of health utility scores (where 1 = 'perfect health', 0 = 'dead'). Owing to the absence of direct evidence of the utility of patients receiving bevacizumab and other chemotherapy regimens, systematic searches were undertaken to identify indirect evidence in order to estimate the utility associated with various states of health for patients with metastatic colorectal cancer.[3] Health utility for patients prior to disease progression was assumed to be 0.80, based on a study by Ramsey et al.[8] Health utility following disease progression was assumed to be 25% (utility = 0.60) lower than the progression-free health state, based on a study reported by Petrou and Campbell.[9] The expected number of QALYs for each treatment group was estimated by calculating the time spent without disease progression multiplied by the utility for the progression-free health state plus the time spent following disease progression multiplied by the health utility for the post-progression health state.

2.5. Modelling resource use and costs

Table 3 presents unit cost estimates used within the model. Unit costs of bevacizumab, irinotecan, oxaliplatin, 5-FU, LV and mitomycin were taken from the British National Formulary No. 50.[10] Where multiple products were listed, the least expensive was assumed. Dose wastage was excluded from the analysis. Data relating to the mean number of doses of bevacizumab, irinotecan, 5-FU and LV and the relative dose intensity of each drug administered during first-line treatment within studies AVF2107g and AVF2192g were obtained from the manufacturer's submission to NICE.[11] Evidence concerning the use of second- and subsequent-line therapy regimens was not collected within study AVF2107g of study AVF2192g.[4,5] The model assumes that patients would receive oxaliplatin plus 5-FU/LV as second-line treatment; the mean number of treatment cycles for this regimen were taken from a study reported by Tournigand et al.[12] We further assumed that 10% of patients would subsequently receive third-line treatment with Mitomycin-C plus protracted 5-FU for a period of 2 months. Given the absence of any empirical evidence, assumptions concerning the use of second- and third-line treatment use were applied equally to all four treatment groups and therefore do not affect the resulting cost-effectiveness estimates.

With the exception of information concerning the use of first-line study medications, resource use data were not

Table 3 – Cost parameters used within the model

Model parameter	Mean cost[a]	Source
5-FU acquisition cost per mg	£0.01	BNF
FA acquisition cost per mg	£0.26	BNF
Bevacizumab acquisition cost per mg	£2.31	BNF
Irinotecan acquisition cost per mg	£1.30	BNF
Oxaliplatin acquisition cost per mg	£3.30	BNF
Mitomycin C acquisition cost per mg	£1.85	BNF
Medical oncology outpatient cost per visit	£114.31	[19]
Line insertion cost	£456.36	[13]
Consultation costs per month	£86.13	[14]
Pump cost per cycle	£66.91	[14]
Diagnostic tests and imaging costs per month	£69.66	[15]
Primary care per month	£11.25	[15]
Drug costs per month (non-bevacizumab regimens)	£10.55	[15]
Drug costs per month (bevacizumab regimens)	£11.93	Based on assumption from Roche submission to NICE, 2005
Mean cost hospitalisation per month (non-bevacizumab regimens)	£277.94	[16]
Mean cost hospitalisation per month (non-bevacizumab regimens)	£314.07	Based on assumption from Roche submission to NICE, 2005
Pharmacy costs per cycle bevacizumab + IFL Roswell Park (6 week)	£122.00	Personal communication[b]
Pharmacy costs per cycle IFL Roswell Park (6 week)	£84.00	Personal communication[b]
Pharmacy costs per cycle bev+5-FU/LV Roswell Park (8 week)	£84.00	Personal communication[b]
Pharmacy costs per cycle 5-FU/LV Roswell Park (8 week)	£46.00	Personal communication[b]
Pharmacy costs per cycle 5-FU/LV MdG + oxaliplatin OP (2 week)	£152.00	Personal communication[b]
Pharmacy costs per cycle mitomycinC+5-FU/LV	£251.00	Personal communication[b]
Best supportive care cost	£600.52	[17]

a Uplifted to 2004 prices.
b Personal communication, Michelle Rowe, The NHS Christie Trust, 2005.

collected within either study AVF2107g or AVF2192g.[4,5] The costs of drug administration, infusional pumps, line insertion, pharmacy preparation and dispensing, adverse event management, diagnostic tests and imaging, clinical and primary care consultations and end-of-life costs were sourced from systematic searches of the literature.[13–18] Hospital attendances for treatment administration were assumed to take place in an outpatient setting; the cost of a medical oncology outpatient visit was taken from Netten and Curtis.[19] Additional resources required to manage bevacizumab-related adverse events were modelled using a relative risk of 1.13 relative to non-bevacizumab-including regimens, based on evidence from the manufacturer.[11] All costs were uplifted to 2005 values using the Health Service Inflation indices.

2.6. *Sensitivity analysis*

Simple sensitivity analysis was undertaken to explore the impact of twelve alternative scenarios on the cost-effectiveness of bevacizumab, as described below.

- *Scenario 1*: Using utility scores for both progression-free and post-progression health states based on the FOCUS trial.[20]
- *Scenario 2*: Assuming post-progression utility is equal to base case pre-progression utility (0.80).
- *Scenario 3*: Assuming the relative reduction in post-progression versus pre-progression utility assumed to be 50%.
- *Scenario 4*: Assuming differential benefits of second-line therapy between treatment groups, based on trial outcomes reported by Tournigand et al.[12]
- *Scenario 5*: Using other lower published cost estimates than those assumed within the base case model.
- *Scenario 6*: Assuming that 5-FU/LV is given according to modified de Gramont regimen.
- *Scenario 7*: Assuming a higher day case cost of £255 .[21]
- *Scenario 8*: Assuming best supportive care costs are £300 per month.
- *Scenario 9*: Assuming best supportive care costs are £1200 per month.
- *Scenario 10*: Assuming all cyclical treatment costs are 25% higher than those used in the base case analysis.
- *Scenario 11*: Assuming all cyclical treatment costs are 25% lower than those used in the base case analysis.
- *Scenario 12*: Fifty percent reduction in bevacizumab acquisition cost.

Probabilistic sensitivity analysis was undertaken to explore the impact of the joint uncertainty surrounding all model parameters. This analysis was undertaken by assigning probability distributions to all uncertain model parameters and subsequently propagating this uncertainty through the model using Monte Carlo sampling techniques to produce information on the likelihood that each intervention produces the greatest amount of net benefit. The results of these simulations are presented as cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs).

3. Results

Table 4 presents the central estimates of cost-effectiveness for the two modelled comparisons. Treatment with bevacizumab plus IFL is estimated to cost approximately £19,361 more than IFL alone over the lifetime of the average patient, and is expected to produce an estimated 0.41 additional LYGs. The model suggests that bevacizumab in combination with IFL costs an estimated £46,854 for each additional LYG when compared to IFL alone. When survival is adjusted to account for differences in health-related quality of life between pre- and post-progression disease states, the addition of bevacizumab to IFL is estimated to produce an additional 0.31 QALYs. The model suggests that bevacizumab in combination with IFL costs an estimated £62,857 per QALY gained when compared to IFL alone. Treatment with bevacizumab plus 5-FU/LV costs approximately £15,615 more than treatment with 5-FU/LV alone over the lifetime of the patient, and results in an estimated 0.19 additional LYGs. The model suggests that bevacizumab in combination with 5-FU/LV costs an estimated £84,396 per LYG when compared to 5-FU/LV alone. When survival is adjusted to account for differences in quality of life between disease states, the addition of bevacizumab to 5-FU/LV is estimated to produce an additional 0.18 QALYs. The model suggests that bevacizumab in combination with 5-FU/LV costs an estimated £88,436 per QALY gained when compared to 5-FU/LV alone.

Table 5 details the results of the simple sensitivity analysis. The sensitivity analysis results suggest that both comparisons are relatively insensitive to changes in the majority of model parameters. The key determinants of cost-effectiveness are the assumptions concerning the level of health utility associated with the pre-progression and post-progression health states, and more importantly, the acquisition cost of

Table 4 – Central estimates of cost-effectiveness

Treatment arm	Mean LYG	Mean QALYs gained	Mean total cost	Marginal cost per LYG	Marginal cost per QALY gained
Study AVF2107g					
Bevacizumab + IFL	1.98	1.44	£43,140	£46,853	£62,857
IFL + placebo	1.57	1.13	£23,779		
Difference	0.41	0.31	£19,361		
Study AVF2192g					
Bevacizumab+5-FU/LV	1.59	1.19	£37,074	£84,396	£88,436
5-FU/LV	1.41	1.01	£21,459		
Difference	0.19	0.18	£15,615		

Table 5 – Simple sensitivity analysis results

Scenario	Marginal cost per QALY (bevacizumab + IFL versus IFL)	Marginal cost per QALY (bevacizumab + 5-FU/LV versus 5-FU/LV)
Base case scenario	£62,857	£88,436
1. Utility scores based on FOCUS trial	£63,316	£114,048
2. Utility score for post-progression assumed to be 0.80	£58,567	£105,495
3. Relative reduction in post-progression versus pre-progression utility assumed to be 50%	£67,826	£76,126
4. Differential benefits of second-line treatment following progression	£63,273	£87,766
5. Lower published cost estimates	£60,805	£84,734
6. 5-FU/LV given according to modified de Gramont regimen	£60,431	£73,849
7. Day case cost = £255	£68,640	£97,815
8. Best supportive care costs = £300 per month	£61,536	£91,352
9. Best supportive care costs = £1200 per month	£65,492	£82,620
10. All costs assumed to 25% higher than base case	£65,863	£90,741
11. All costs assumed to 25% lower than base case	£59,851	£86,131
12. 50% reduction in bevacizumab acquisition cost	£38,738	£53,814

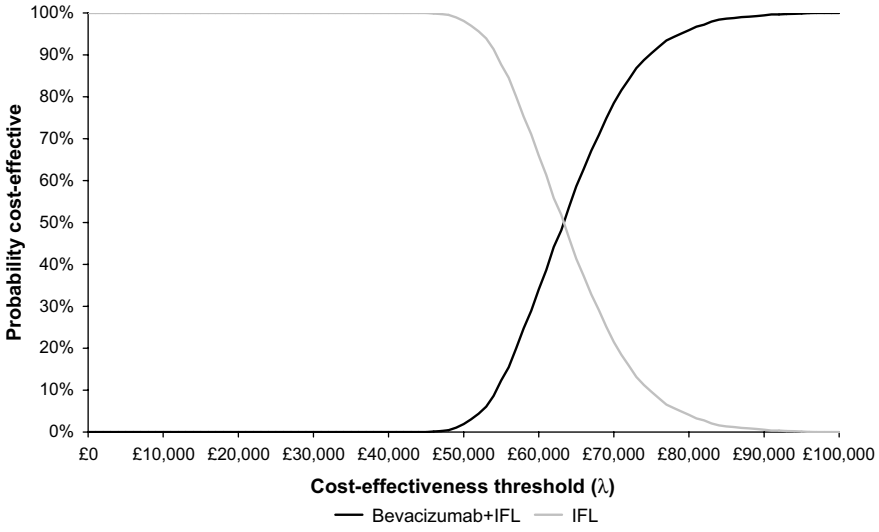

Fig. 2a – Marginal CEAC for bevacizumab plus IFL versus IFL.

bevacizumab. Interestingly, the impact of changing assumptions concerning the quality of life associated with the post-progression health state do not have a consistent impact across the two models. For the IFL comparison, the addition of bevacizumab resulted in an expected improvement in progression-free survival of around 0.30 years, and an improvement in overall survival of around 0.41 years. However, for the 5-FU/LV comparison, the relationship between progression-free survival and overall survival was reversed, as the improvement in progression-free survival was greater than that for overall survival for patients receiving bevacizumab. The sensitivity analysis whereby the acquisition cost of bevacizumab was reduced by 50% resulted in considerably more favourable cost-effectiveness ratios for both indications of bevacizumab. However, none of the analyses resulted in cost-effectiveness ratios for bevacizumab that are likely to be considered acceptable to UK policymakers.

The results of the probabilistic sensitivity analysis are presented as marginal CEACs in Figs. 2a and 2b. The CEACs suggest that the probability that the cost-effectiveness of bevacizumab in either combination is better than £30,000 per QALY gained is close to zero.

4. Discussion

The results of the health economic analysis suggest that the marginal cost-effectiveness of bevacizumab in combination with IFL is approximately £62,857 per QALY gained, whilst the marginal cost-effectiveness of bevacizumab in combination with 5-FU/LV is approximately £88,436 per QALY gained. Unsurprisingly, the key determinant of cost-effectiveness and cost-utility is the acquisition cost of bevacizumab. Neither indication of bevacizumab is likely to represent value for money for the NHS.

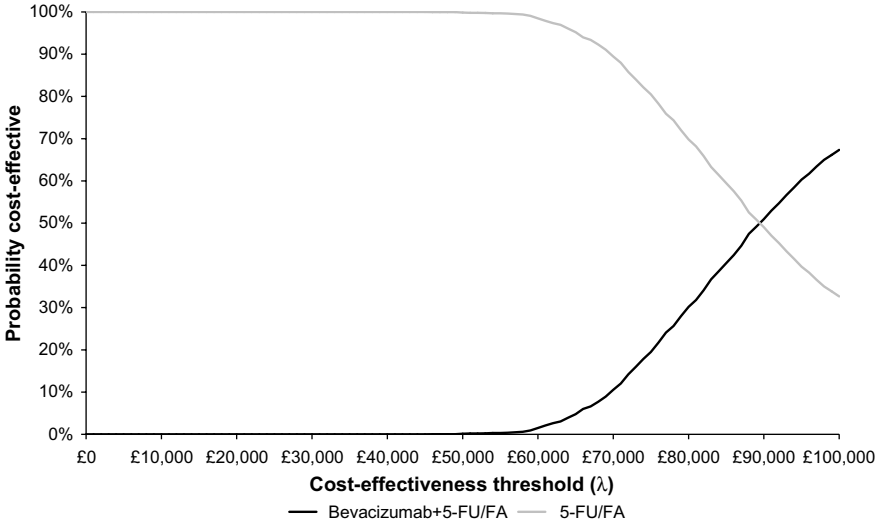

Fig. 2b – Marginal CEAC for bevacizumab plus 5-FU/LV versus 5-FU/LV.

It should be noted that the models developed within this study are subject to some limitations. Within the two key bevacizumab RCTs, which form the basis of the model,[5,6] treatment was administered according to the Roswell Park regimen whereby patients received bolus 5-FU/LV once weekly for four out of every six weeks,[5] or for six out of every eight weeks.[6] These regimens may have different effectiveness profiles and resource implications to the typical infusional 5-FU/LV regimens, which are commonplace in clinical practice in the UK. As such, the external validity of the model may be limited. Furthermore, whilst the sensitivity analysis attempted to explore the likely impact of using bevacizumab in combination with infusional regimens, this analysis assumed that progression-free survival and overall survival outcomes for bolus and infusional regimens are equivalent; this assumption may not be justified. In addition, preference-based utility scores were not collected within the RCTs of bevacizumab, hence assumptions concerning the level of health-related quality of life associated with the presence or absence of disease progression were sourced from indirect sources. The sensitivity analysis demonstrates that these parameters do have the capacity to affect the cost-effectiveness of both indications of bevacizumab. Finally, evidence concerning resource use following disease progression was not collected within either study AVF2107g[5] or AVF2192g,[6] hence we assumed that subsequent resource use following progression was independent of first-line therapy. Importantly, the source of all of these limitations can be found in the evidence base, not the model.

Existing uncertainties surrounding the use of bevacizumab in the treatment of metastatic colorectal cancer give rise to four potential areas for further research.

- Further clinical research studies are required to evaluate the true impact of first-line bevacizumab in combination with irinotecan and/or infusional 5-FU/LV on overall survival in patients with metastatic CRC who are representative of the typical population of CRC patients in England and Wales.
- Further research concerning the impact of treatment with bevacizumab on quality of life is indicated; such research may be undertaken as part of an RCT.
- Evidence concerning the specific resource implications associated with bevacizumab would be valuable.

5. Conclusions

The health economic evaluation suggests that the cost-effectiveness of bevacizumab plus chemotherapy is unlikely to be lower than around £60,000 per QALY gained. Consequently, bevacizumab is unlikely to represent a cost-effective use of NHS resources in England and Wales. Further research is indicated to improve existing information concerning the impact of bevacizumab on clinically relevant parameters, particularly survival and quality of life, when used in combination with infusional chemotherapy regimens.

Conflict of interest statement

None declared.

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