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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Bevacizumab in combination with fluoropyrimidine-based chemotherapy for the first-line treatment of metastatic colorectal cancer

Roche Submission to the
National Institute for Health and Clinical Excellence
Submitted: 23rd July 2009

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Abbreviation	Full name
AE	Adverse event
AUC	Area under the curve
BNF	British National Formulary
B-XELOX	Bevacizumab in combination XELOX
B-FOLFOX-4	Bevacizumab in combination with FOLFOX-4
B-FOLFOX-6	Bevacizumab in combination with FOLFOX-6
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
dG	de Gramont
ECOG	PS Eastern Co-operative Oncology Group Performance
EGFR	Epidermal growth factor receptor 1 (also
EMEA	European Medicines Evaluation Agency
EQ-5D	Euro QOL questionnaire
ERG	Evidence review group
EU	European union
FOLFIRI	irinotecan in combination with leucovorin and 5-FU (mG)
FOLFOX-4	oxaliplatin in combination with leucovorin and 5-FU (mG)
FOLFOX-6	oxaliplatin in combination with leucovorin and 5-FU (mdG)
HR	Hazard ratio
ICER	Incremental cost effectiveness ratio
ITT	Intention to treat
IV	Intravenous
LY	Life year
LYG	Life year gained
mg/m2	Milligram per meter squared
mg/kg	Milligram per kilogram
mdG	Modified de Gramont
N/A	Not applicable
NCI	National Cancer Institute
NE	Not Evaluable
NR	Not recorded /reported
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PFS_T	Progression-free survival on treatment
PFS_{PT}	Progression-free survival on post treatment
PD	Progressive disease
PR	Partial response

Abbreviation	Full name
PS	Performance status
QALY	Quality adjusted life year
RCT	Randomised Controlled Trial
RDI	Relative dose intensity
RECIST	Solid evaluation criteria in solid tumours
SAE	Serious adverse event
SG	Standard gamble
SmPC	Summary of product characteristics
TA	Technology appraisal
TTP	Time to progression
XELOX	Oxaliplatin in combination with capecitabine

Section A

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the 'Guide to the single technology appraisal process' – www.nice.org.uk). A (draft) Summary of Product Characteristics (SPC) for pharmaceuticals and a (draft) technical manual for devices should be provided (see appendix 1, section 9.1).

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device

Brand Name: Avastin

Approved Name: Bevacizumab

Therapeutic class: Antineoplastic, antiangiogenic monoclonal antibody.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates)

Yes – bevacizumab (Avastin) was first approved for use for the treatment of metastatic colorectal cancer (CRC) in January 2005. The original Marketing Authorisation covered the use of bevacizumab in conjunction with IV 5-FU +/- irinotecan . On January 25th 2008 this indication was broadened as described in Section 1.3. In effect, this allowed bevacizumab to be used in conjunction with other important chemotherapy regimens used for colorectal cancer – combinations of fluoropyrimidines plus oxaliplatin, which are the subject of this appraisal.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The current indications for bevacizumab throughout the EU, including the UK are as follows:

- Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum. This is the subject of the current submission.

- Bevacizumab in combination with paclitaxel is indicated for first-line treatment of patients with metastatic breast cancer.

- Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology

- Bevacizumab in combination with interferon alfa-2a is indicated for first-line treatment of patients with advanced and/or metastatic renal cell cancer.

There is an extensive ongoing clinical development programme for bevacizumab which it is anticipated will result in the addition of a variety of additional indications to the product's Marketing Authorisation including the treatment of glioblastoma multiform, ovarian cancer and early bowel, breast and colorectal cancers. Further details of the bevacizumab development programme have already supplied to the NHSC Horizon Scanning team and can be supplied separately to NICE on request.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

There is currently minimal NHS usage of bevacizumab in metastatic colorectal cancer. In most developed countries outside of the UK, the combination of chemotherapy plus bevacizumab is considered (on the basis of existing clinical evidence) one of the standard treatments for the first-line treatment of metastatic colorectal cancer. Clinical studies of chemotherapy +/- bevacizumab in metastatic colorectal cancer are therefore of little scientific interest and ethically problematic, new studies of this type are unlikely. However, because chemotherapy plus bevacizumab is widely accepted as a benchmark regimen, it may be being used as the control arm of studies testing novel agents added to chemotherapy.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Yes- bevacizumab has regulatory approval for the treatment of metastatic colorectal cancer in most countries of the world, including all of the EU, the US, Australia and Canada. Specific details on regulatory status in specific countries of interest can be provided on request.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

In June 2008, the Scottish Medicines Consortium issued guidance (No. 469/08) rejecting first-line use of the combination of bevacizumab plus a fluoropyrimidine plus oxaliplatin as first-line treatment for metastatic colorectal cancer. Clinical effectiveness was not disputed. However at the time patient access schemes were not able to be considered by the SMC and the intervention was rejected on cost-effectiveness grounds. We intend to make a resubmission to the SMC for this indication with the same patient access scheme which is proposed for England and Wales.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Vials containing 25mg mg per ml – 100mg in 4 ml and 400 mg in 16ml.

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

It is proposed that patients with metastatic CRC who would currently receive FOLFOX or XELOX chemotherapy should, also receive bevacizumab (B-FOLFOX or B-XELOX). The proposed dose of bevacizumab is 5 mg/kg bodyweight by intravenous infusion every 2 weeks with FOLFOX or 7.5 mg/kg every 3 weeks with XELOX. In both cases treatment is continued from the start of chemotherapy until disease progression or unacceptable toxicity and not repeated i.e. limited to a single course. In the event of treatment with chemotherapy being ceased due to chemotherapy related toxicity, it is recommended that treatment with bevacizumab be continued until progression.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The unit cost of bevacizumab to the NHS at current NHS list price is as follows:-

100 mg vial, £242.66

400 mg vial £924.40.

However, Roche is submitting a Patient Access Scheme with this NICE submission which will specifically cover the use of bevacizumab in combination with oxaliplatin-based chemotherapy. Further details of this scheme are provided in Section 2,

special considerations. The patient access scheme has at the time of submission not been approved by DH but a decision is expected imminently.

1.10 What is the setting for the use of the technology?

Bevacizumab is administered by IV infusion during the same treatment episode as IV oxaliplatin. As such the treatment setting for bevacizumab is wherever IV oxaliplatin is administered. Currently, this is largely in the hospital outpatient setting. However, there is some use of oxaliplatin in the homecare setting delivered by homecare providers. Capecitabine is administered orally and 5-FU is delivered as a protracted IV infusion, typically started in the hospital day-case unit, with the patient continuing treatment for 48 hours at home.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

There is no absolute requirement for additional tests prior to the addition of bevacizumab to chemotherapy regimens for metastatic colorectal cancer or during treatment. However, since bevacizumab may cause hypertension and proteinuria it may be considered prudent to measure blood pressure and dip-stick test urine for protein prior to prescribing. These tests have minimal cost or impact on patients and the NHS.

During treatment, periodic measurement of blood pressure, particularly early in treatment is prudent but can readily be incorporated into regular clinic visits as can dip-stick testing of urine.

When bevacizumab is administered with a fluoropyrimidine and oxaliplatin for the treatment of metastatic colorectal cancer, it can be given on the same day as IV oxaliplatin. By doing this no additional treatment appointments are required. It is recommended that the first infusion is give over 90 minutes, with the infusion time reduced to 60 minutes and then 30 minutes for the second and third or subsequent doses. Therefore, the addition of bevacizumab will extend IV oxaliplatin treatment episodes by 90 minutes on the first occasion falling, in most cases, to 30 minutes by the third dose.

Monitoring of treatment response is the same for patients receiving chemotherapy regardless of whether or not they receive concomitant bevacizumab.

No co-medications are mandated during bevacizumab therapy, but for the minority of patients who experience unacceptable hypertension, antihypertensive therapy may need to be instituted or reviewed.

2 Statement of the Decision Problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable	The Avastin Marketing Authorisation permits bevacizumab use with oxaliplatin-based chemotherapy at any line of therapy. However, Roche will be seeking positive recommendation for these combinations in first-line only. Reasons for the emphasis on first-line treatment are provided in note 1 below.
Intervention	Bevacizumab in combination with oxaliplatin and either 5-FU or capecitabine	As per scope
Comparator(s)	Oxaliplatin-including chemotherapy regimens without bevacizumab Irinotecan-including chemotherapy regimens without bevacizumab	**Primary Emphasis** Oxaliplatin-including chemotherapy regimens without bevacizumab **Secondary Emphasis** Comparison *vs* Irinotecan-based regimens are considered of limited clinical relevance. (see note 2 below) However for completeness an economic comparison has been performed *vs* irinotecan-based therapy given there may be a small number of patients for whom this comparison is relevant.

Outcomes	overall survival progression-free survival response rate adverse effects of treatment health-related quality of life	As per scope
Economic Analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per scope
Subgroups to be considered	None specified	Consideration will be given to the activity of bevacizumab in patients with isolated liver metastases because the recent Cetuximab guidance from NICE has defined this as a group where a different approach to drug therapy may be required.

Special considerations, including issues related to equity or equality	Roche will be submitting a Patient Access Scheme with this appraisal for patients receiving bevacizumab plus oxaliplatin-based chemotherapy. The PAS is likely to consist of bevacizumab supplied at a fixed price per administration, with the cost of bevacizumab being capped at a fixed number of treatment months per patient and with oxaliplatin being provided free of charge throughout. This scheme design is subject to modification as it has not yet been approved by DH but this is nearing completion at the time of submission

Decision Problem Notes

1. Focus on first-line chemotherapy setting

The only direct randomised trial evidence (E3200 study) for adding bevacizumab to oxaliplatin-based chemotherapy in relapsed disease uses a dose of bevacizumab twice that proposed in this submission for routine UK usage. The clinical effectiveness of adding bevacizumab to oxaliplatin based therapy was clearly demonstrated using this "high dose" regimen in the 2nd line setting and the results will be presented in this submission. However, in advance of performing a detailed cost-effectiveness analysis a rudimentary model was constructed to estimate an approximate cost per QALY utilising the "high dose" used in the E3200 study. Based on the results of this analysis, Roche does not expect to be able to present a cost-effective case in the 2nd line setting (applying NICE's criteria) and hence a more

comprehensive analysis has not been performed. The methods and results of the second-line analysis have been included in the submission.

2. Treatment of irinotecan as a comparator

It is considered that comparison of bevacizumab in combination with oxaliplatin-based therapy compared to irinotecan-based therapy is of limited clinical relevance for the following reason. Irinotecan-based chemotherapy is now a minority first-line treatment in the UK (Market Research; Synovate for Roche, 2009; see Table 3), largely restricted to patients where oxaliplatin is contraindicated, so that only a very small number of patients currently receiving irinotecan-based therapy would be suitable for bevacizumab in combination with oxaliplatin.

From a cost-effectiveness perspective irinotecan as a separate comparator is also of limited relevance. In a previous NICE appraisal the Appraisal Committee concluded that it would not differentiate between oxaliplatin- and irinotecan-based therapies in terms of clinical effectiveness and that the confidence intervals around the cost of these regimens overlapped substantially [section 4.3.5 FAD TA93]. Hence one could assume that the cost per QALY when bevacizumab plus oxaliplatin-based chemotherapies are compared to irinotecan-based regimens would be similar to the cost per QALY achieved when comparing oxaliplatin-based chemotherapy plus bevacizumab with oxaliplatin-based chemotherapy alone as explored in the primary analysis.

Subsequent to TA93 being published a mixed treatment comparison (MTC) comparing the chemotherapy regimens of interest was published, and so for completeness, the relative clinical efficacy of irinotecan is discussed in light of the results of this MTC in section 6.6, and an approximate estimate of the cost per QALY versus irinotecan has been calculated based on these results.

Section B

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

Background

Metastatic colorectal cancer (mCRC) is, in the majority of cases, incurable and treatment is palliative in nature. Although local radiotherapy and, less commonly, surgery, both have a role, metastatic disease is essentially a systemic disease requiring systemic treatment. With current standard first-line chemotherapy, median survival is around 15-20 months.

Bevacizumab (brand name: Avastin) was the first in an innovative class of drugs that act as anti-angiogenic agents. Angiogenesis inhibitors are drugs which are designed to stop tumours from developing a blood supply, a pre-requisite for tumour growth and metastasis (tumour spreading). Bevacizumab works by inhibiting the action of VEGF, a specific angiogenesis growth factor that binds to receptors on blood vessels and stimulates the formation of new blood vessels. By binding to VEGF, bevacizumab blocks VEGF binding to its receptors. Since its launch in January 2005, bevacizumab has become the standard of care for 1st line mCRC in the vast majority of developed countries.

In June 2007, NICE recommended in TA118 that bevacizumab should not be added to first-line chemotherapy of metastatic colorectal cancer with 5-FU plus FA+/- irinotecan. Whilst the Appraisal Committee acknowledged the clinical benefits of bevacizumab (median increase of 4.7 months OS when adding bevacizumab to 5-FU plus FA + irinotecan) they had concerns over the cost-effectiveness of its use, which was estimated to result in a cost per QALY of £62,857 when bevacizumab was added to 5-FU plus FA + irinotecan.

The most recent update to the bevacizumab Marketing Authorization for CRC (January 2008), based upon the NO16966 phase III RCT, makes it less prescriptive in the chemotherapy regimens bevacizumab may be combined with. Consequently the license now states *"Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum".* This allows new bevacizumab based interventions for CRC patients, with a different profile of costs and outcomes therefore requiring a new economic evaluation and assessment. A patient access scheme (APAS) has been designed so that bevacizumab in combination with oxaliplatin-based regimens will meet NICE's criteria for cost-effectiveness when compared to current best practice in the UK. All cost-effectiveness analyses presented in the submission were performed within the context of APAS.

This submission dose not attempt to represent a case for bevacizumab in combination with irinotecan based therapy which is the subject of existing guidance (TA118).

Proposed use of Bevacizumab

The XELOX and FOLFOX regimens represent the vast majority of first-line combination treatment for patients with mCRC in England and Wales. Only a minority of patients receive FOLFIRI, most of whom are likely to be unsuitable for oxaliplatin treatment. Hence XELOX and FOLFOX are the main comparators of interest.

It is proposed that patients with metastatic CRC who would currently receive FOLFOX or XELOX chemotherapy should also receive bevacizumab (B-FOLFOX or B-XELOX). The proposed dose of bevacizumab is 5 mg/kg bodyweight by intravenous infusion every 2 weeks with FOLFOX or 7.5 mg/kg every 3 weeks with XELOX. In both cases treatment is continued from the start of chemotherapy until disease progression or unacceptable toxicity and not repeated i.e. limited to a single course.

In the UK bevacizumab is available in vials containing 100mg (25mg per ml in a 4 ml vial) at a list price of £242.66 and 400 mg (25mg per ml in a 16ml vial) for £924.40.

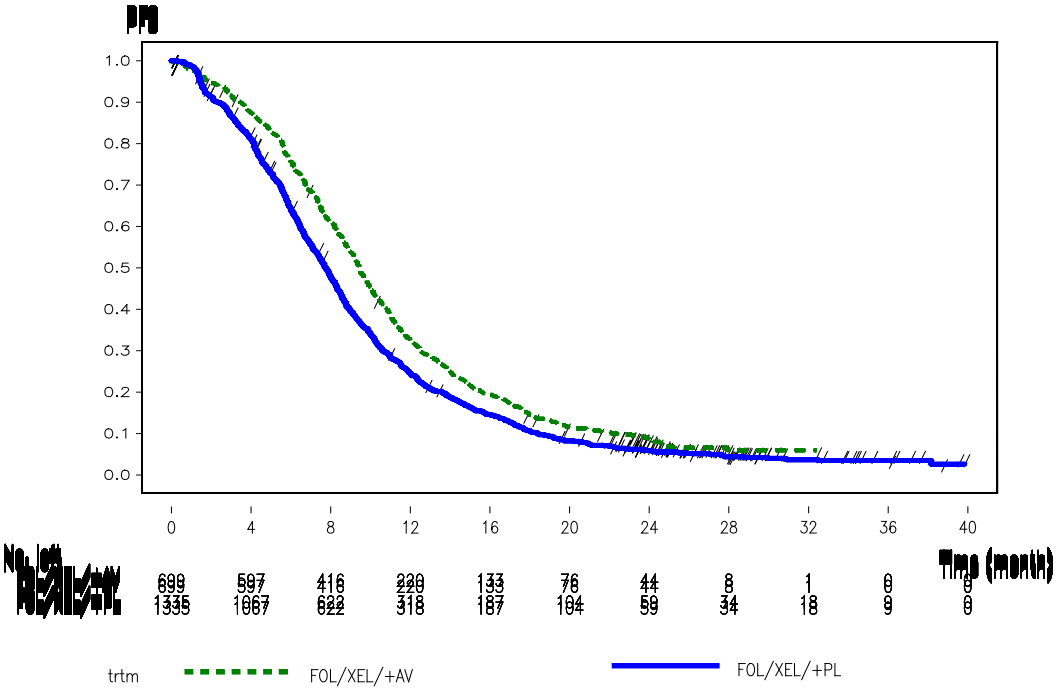
The dose of bevacizumab administered is based on the patient's weight, however in the APAS the price of bevacizumab is charged at a fixed price per cycle irrespective of the number of vials consumed. The price per cycle is £1200 and £800 for the 3 weekly XELOX-based regimen and 2 weekly FOLFOX-based regimen respectively for the first 12 months of treatment and then supplied free of charge for the remaining duration of 1st line treatment.

Clinical Effectiveness

This submission is based primarily on the NO16966 study, a large phase III randomised controlled clinical trial (RCT), which formed the basis of the regulatory submission to the EMEA resulting in the extension to the Marketing Authorisation for Avastin that prompted this Appraisal. The co-primary study end-points were, firstly, superiority of PFS (assessed on an intent-to-treat [ITT] basis) in patients receiving chemotherapy (XELOX or FOLFOX) plus bevacizumab *versus* those receiving chemotherapy alone. The second-co-primary endpoint was non-inferiority of PFS in the population receiving XELOX (with or without bevacizumab or placebo) *versus* those receiving FOLFOX (with or without bevacizumab).

The NO16966 study met both of its co-primary endpoints. In the pooled ITT comparison of chemotherapy plus bevacizumab (B-XELOX/B-FOLFOX) *versus* chemotherapy alone (XELOX/P-XELOX/FOLFOX/P-FOLFOX) which forms the basis of the cost-effectiveness part of this submission the risk of disease progression was reduced by 21% (HR=0.79, 95% CI 0.72, 0.87; p=0.0001) and median PFS increased from 7.7 to 9.4 months (increase of 1.7 months). The addition of bevacizumab also significantly improved OS. The risk of death was reduced by 17% (HR=0.83, 97.5% CI 0.74, 0.93; p=0.0019) and median OS increased from 18.9 to 21.2 months (increase of 2.3 months). Kaplan-Meier plots for PFS and OS are displayed below.

Figure 1: Improvement in progression-free survival when bevacizumab was added to oxaliplatin-based chemotherapy in study NO16966



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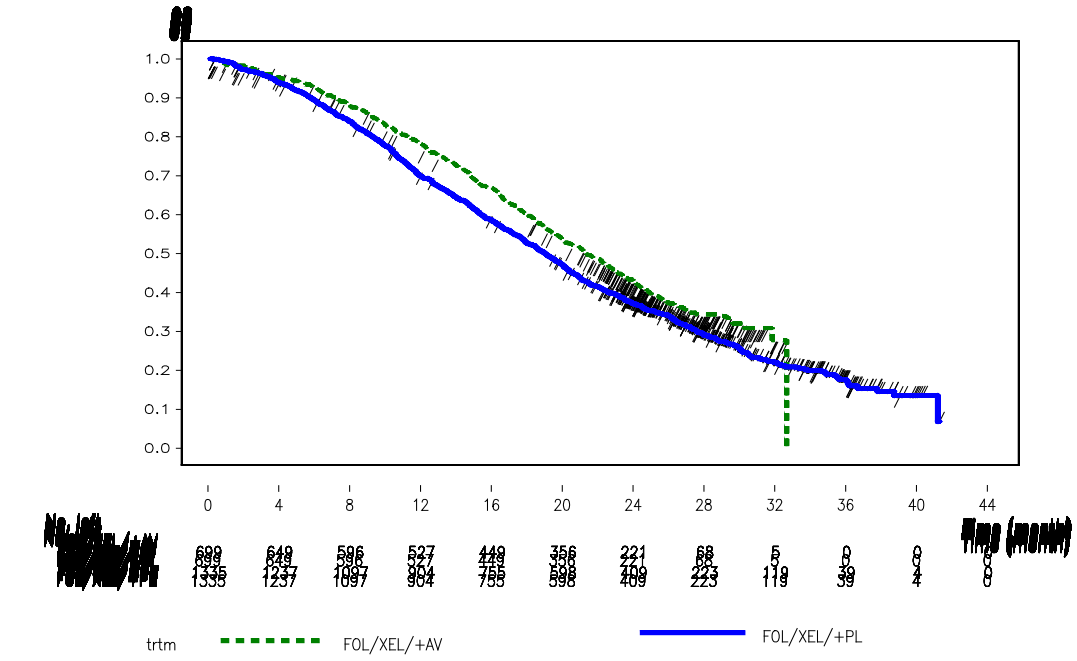
16JUL2009 17:45

Abbreviations: F, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-XELOX; X+P, P-XELOX;

Figure 2: Improvement in overall survival when bevacizumab was added to oxaliplatin-based chemotherapy in study NO16966



Abbreviations: F, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-XELOX; X+P, P-XELOX;

The results of the NO16966 study are supported by results from the ECOG3200 second-line RCT, TREE (a non-randomised study), and both a meta-analyses by Cao *et al.* 2009 and a comprehensive independent mixed-treatment comparison by Golfinopoulos *et al* 2007. All of these studies demonstrated that adding bevacizumab to chemotherapy (including that based on oxaliplatin) consistently and convincingly improves survival by a clinically meaningful extent.

The comprehensive safety data collected in study NO16966 and elsewhere, and meta-analysed by Cao *et al* (2009), demonstrated that B-XELOX and B-FOLFOX has similar tolerability to FOLFOX and XELOX.

Demonstrating the Cost-Effectiveness of Bevacizumab

The economic evaluation was performed accounting for the Avastin Patient Access Sceheme (APAS) and hence all figures presented below represent the results in the context of this scheme.

The evaluation was based on an incremental cost-utility analysis designed to compare the costs and outcomes of each of the interventions of interest, primarily B-XELOX, B-FOLFOX, XELOX and FOLFOX. For completeness comparison *versus* FOLFIRI was also evaluated.

The economic evaluation conforms to the reference case as described in NICE's Guidance to the Methods of Technology Appraisal. The economic model developed

was a four-state area under the curve model, where patients are assumed to be within one of four possible discrete health states at any given time; “first-line treatment”, “progression-free survival”, “progressed” or “death”. This analyis was based on the relatively mature data set from the NO16966 study. The vast majority of patients had progressed at the point of follow-up and therefore relatively little extrapolation was required to estimate mean progression-free survival. At the point of latest follow-up 39.9% and 27.6% of patients were still alive in the bevacizumab-containing arms and chemotherapy alone arms respectively, hence overal survival was extrapolated using parametric methods. First-line treatment duration, dose intensity, and adverse event incidence was also taken from the NO16966 study.

The variant of the FOLFOX regimen used in the NO16966 study was FOLFOX-4 whereas the most used FOLFOX variant in England and Wales is FOLFOX-6 (Expert Opinion). FOLFOX-6 is considered to offer equivalent efficacy to FOLFOX-4 whilst being less resource intensive to deliver; patients are only required to attend hospital for infusions once per 2 weekly cycle as opposed to twice with the FOLFOX-4 regimen. An analysis was thus performed for both FOLFOX-4 and -6 with and without bevacizumab.

The comparison *versus* FOLFIRI was informed by the mixed-treatment comparison by Golfinopoulos et al *(*2007).

The combination of bevacizumab with oxaliplatin and either 5-FU / capecitabine resulted in a mean gain of 2.9 months of life compared with 5-FU/capecitabine in combination with oxaliplatin alone. Compared with FOLFIRI, the bevacizumab combination therapy resulted in an increase of 4.0 months of life.

XELOX resulted in the lowest total cost of all the regimens with a total cost per patient of £[redacted]. Total cost for B-XELOX was [redacted] representing the least expensive of the bevacizumab regimens. The incremental total costs for each comparator *versus* each intervention are show below.

Table 1: Mean Incremental cost per patient

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

B-XELOX resulted in the same QALYs gained but was less costly than B-FOLFOX and thus was the dominant bevacizumab containing regimen. XELOX dominated the regimens that did not contain bevacizumab. Hence XELOX and B-XELOX make up the cost effectiveness frontier (see below).

Figure 3: Economic results plotted on cost effectiveness plane

Comparing the two regimens on the efficiency frontier, B-XELOX and XELOX, resulted in an incremental cost per QALY of £34,170.

A small number of patients however may not be suitable for capecitabine making the incremental cost effectiveness of adding bevacizumab to the oxaliplatin containing therapy they currently receive also of relevance. Adding bevacizumab to FOLFOX-6, the most used FOLFOX based regimen in England and Wales (Expert Opinion) resulted in an ICER is £41,388.

When B-XELOX relplaces the currently most used comparator regimen in England and Wales FOLFOX-6 (Market Research; Synovate for Roche, 2009) the ICER was £594.

B-XELOX and B-FOLFOX-6 may also be considered cost effective when replacing FOLFIRI, for patients that are suitable for oxaliplatin-based regimens, with a cost per QALY gained of £9,192 for B-XELOX vs FOLFIRI mdG and £38,835 for B-FOLFOX-6 vs FOLFIRI mdG.

Table 2: Mean ICERs (£/QALY) per patient

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	£34,170	£594	Dominant	£9,192	Dominant
B-FOLFOX-6	£75,211	£41,388	£22,958	£38,835	£22,292
B-FOLFOX-4	£102,434	£68,154	£50,307	£58,575	£42,031

Summary

A large well-designed randomised controlled trial demonstrated that for patients with mCRC, who need treatment for the first time, adding bevacizumab to oxaliplatin-based chemotherapy significantly increases efficacy compared to oxaliplatin-based chemotherapy alone. The addition of bevacizumab to either XELOX or FOLFOX is estimated to extend patients life by an average of 2.9 months where currently their life expectancy is less than two years. These results are further supported by data from the E3200 second-line study, TREE, and mixed-treatment- and meta-analyses.

These important benefits are achieved with minimal extra burden of treatment being put upon patients, and with minimal additional toxicity relating to the addition of bevacizumab. Furthermore the quality of life of patients treated with bevacizumab will be enhanced by a prolonged first remission of their disease.

The economic evaluation indicates that adding bevacizumab to the current standard of care in the UK (FOLFOX or XELOX) is a cost-effective treatment option, which we believe represents an efficient use of NHS resources.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

Typical of an industrialised country, the UK has high rates of colorectal cancer. In 2005 there were 36,766 new cases of colorectal cancer, and it was the 3rd most common cancer (Cancer Research UK, 2009a). If colorectal cancers are detected when confined to the bowel wall and local lymph nodes (Dukes Stage A, B or C, American Joint Committee on Cancer-AJCC-Stage 1-3) the primary treatment is surgical excision. In patients with Dukes' C tumours there is clear evidence for the value of a course of post-operative adjuvant chemotherapy to reduce the risk of disease recurrence, and such treatment has been part of standard care in the UK since at least 2004 when it was recommended in the NICE clinical guideline on management of colorectal cancer (NICE, 2004). There is also evidence of a smaller benefit from adjuvant chemotherapy to patients who have had a Dukes' B tumour removed and many clinicians extend its use to "high risk" Dukes'B patients (e.g. those with aggressive histology or large tumours).

Although better surgical treatment and improved adjuvant therapy have both contributed to a decline in mortality from colorectal cancer, the 5-year survival is still only just over 50% (Cancer Research UK, 2009b). This is a consequence of the fact that most patients are either diagnosed with disease that has already spread to sites distant from the bowel (metastasised) or relapse with secondary tumours outside the bowel as a result of the growth of microscopic metastatic deposits present, but undetected, at the time of surgery.

Metastatic disease is, in the majority of cases, incurable and treatment is palliative in nature. Although local radiotherapy and, less commonly, surgery, both have a role, metastatic disease is essentially a systemic disease requiring systemic treatment. Traditionally this has meant cytotoxic chemotherapy, though in recent years passive immunotherapy in the form of monoclonal antibody treatment has been added to chemotherapy regimens. With current standard first-line chemotherapy, median survival is around 15-20 months (De Gramont *et al.* 2000; Douillard *et al.* 2000 Giachetti *et al*. 2000; Saltz et al. 2000; Grothey *et al.* 2002; Kohne et al 2003; Tournigand et al. 2004) (Scheithauer *et al.* 1993; Glimelius *et al.* 1995; Beretta *et al.* 1997). This is a considerable improvement over the 6 months typically achieved with symptomatic care alone (Scheithauer *et al.* 1993; Glimelius *et al.* 1995; Beretta *et al.* 1997) and is not at the expense of quality of life which is improved by chemotherapy (Scheithauer *et al.* 1993; Cunningham *et al.* 1999; Glimelius *et al.* 1995).

Since its description by Heidelberger in 1957, the fluoropyrmidine antimetabolite 5-fluorouracil (5-FU) has been the backbone of chemotherapy for colorectal cancer. Administered alone using intravenous (IV) bolus or short infusion schedules the activity of 5-FU is very modest, with response rates as low as 3% (as reviewed by

Grem in 1997). However, over the ensuing half-century the efficacy and convenience of fluoropyrimidine therapy has been improved. Firstly, its short pharmacokinetic half-life was accounted for by extending the 5-FU infusion period (Meta-analysis Group in Cancer, 1998). Next, its efficacy was enhanced by co-administering the potentiating agent calcium folinate (FA) (Piedbois and Michiels, 2003). Most recently IV administered 5-FU has been replaced by the orally-delivered, tumour activated, 5-FU pro-drug, capecitabine. This has now been shown in multiple clinical trials in colorectal (Cassidy *et al*. 2002; Cassidy *et al*. 2006a; Scheithauer *et al*. 2003; Twelves *et al.* 2001; Twelves *et al.* 2005; Van Cutsem *et al*. 2004). As well as upper GI cancers (Cunningham *et al* 2008; Kang *et al.* 2009), to produce the same anti-tumour benefits as contemporary regimens of 5-FU+/-FA. Where it has been reviewed by NICE, capecitabine has been found to represent a cost-effective alternative to infused 5-FU (see TA61, May 2003 and TA100, April 2006). It has also been shown to offer patients an oral treatment option that most prefer (Liu *et al* 1997; Borner *et al* 2002; Twelves *et al* 2006) freeing them as it does from the requirement to an IV infusion pump connected to a permanent venous access for 2 days in every fortnight.

The efficacy of fluoropyrimidine therapy has been further increased by the addition of other cytotoxic agents to treatment regimens. The cytotoxic drugs irinotecan and oxaliplatin are now both well established in the treatment of metastatic colorectal cancer and endorsed by NICE in the first- and second-line settings. In terms of survival outcomes, there is no clearly preferred treatment sequence and NICE allows irinotecan or oxaliplatin to be used at first- and second-line (TA93, 2005).

In practice, according to Roche market research (shown in Table 3) around one-quarter of patients receive fluoropyrimidine monotherapy (mostly capecitabine) first-line for metastatic disease. These patients are those where clinician and/or patient take the view that the additional toxicity conferred by oxaliplatin/irinotecan is unacceptable. Therefore, they are outside the scope of this appraisal which is concerned with patients for whom oxaliplatin-based chemotherapy would currently be prescribed.

Table 3: Chemotherapy regimens used for the first-line treatment of metastatic colorectal cancer in England (Roche commissioned market research conducted by Synovate)

	% First-line treatment		
Regimen	**June 2007**	**June 2008**	**Dec 2008**
Oral Capecitabine monotherapy	27	27	21
Oral Capecitabine plus IV irinotecan (XELIRI)	3	5	4
Oral capecitabine plus IV oxaliplatin (XELOX)	22	21	24
IV 5-FU+/-FA	3	5	4
IV 5-FU+FA+Oxaliplatin (FOLFOX)	15	23	28
IV 5-FU+FA+Irinotecan (FOLFIRI)	20	15	12

Abbreviations: FA, folinic acid; 5-FU, 5-fluorouracil

Of patients currently receiving combination chemotherapy, the majority (76%) receive oxaliplatin plus a fluoropyrimidine. FOLFOX (5-FU, FA, oxaliplatin) has consistently been the most widely used regimen over the last two years, with XELOX

(capecitabine and oxaliplatin) running it a close second. The preference for oxaliplatin over irinotecan is probably the result of two factors:-

- A preference for the toxicity profile of oxaliplatin. The hallmark toxicity of oxaliplatin is cumulative neuropathy (de Gramont *et al*. 2000; Giachetti *et al*. 2000; Grothey *et al*. 2002), which though it can be troublesome to patients is seldom life-threatening, whereas irinotecan produces high rates of profound neutropenia which can result in life-threatening infections, particularly when it occurs in conjunction with the very severe diarrhoea that it also causes and which is, in itself, very unpleasant for patients (Douillard *et al.* 2000; Saltz *et al* 2000; Kohne *et al* 2003).

- For patients and clinicians keen on oral rather than infusional fluoropyrimidine treatment, the data on the irinotecan/capecitabine combination are limited, probably explaining its very low usage and the much higher usage of XELOX relative to XELIRI.

Of the patients who *do* receive irinotecan as part of their first-line chemotherapy for metastatic disease, a significant number are unsuitable for oxaliplatin because their disease is considered resistant to the drug, having progressed during or soon after stopping oxaliplatin-based adjuvant therapy. Oxaliplatin-based chemotherapy dominates adjuvant chemotherapy for patients fit enough to receive it. Roche market research in 2008 showed that 33% and 53% of Stage 2 and 3 patients, respectively, received an adjuvant regimen consisting of a fluoropyrimidine and oxaliplatin, representing 91% and 93% of all combination chemotherapy used in these patient groups. This preference for oxaliplatin in adjuvant treatment is based on superior evidence of efficacy and safety for oxaliplatin over irinotecan in this setting and this situation is unlikely to change following the recent publication of the MOSAIC and PETACC-3 studies confirming the survival benefit of adding oxaliplatin to adjuvant chemotherapy with a fluoropyrimidine (MOSAIC; Andre *et al.* 2009) and failing to show any benefit from adding irinotecan to adjuvant 5-FU/FA (PETACC-3; Van Cutsem *et al*. 2009a)

In addition to those patients whose disease has already demonstrated resistance to adjuvant oxaliplatin, some patients are unsuitable for oxaliplatin in the metastatic setting for other reasons. For example, they may have pre-existing neuropathy, that is likely to be exacerbated by this platinum-based drug. In other words, when account is taken of patients for whom oxaliplatin is contraindicated, this drug plus a fluoropyrimidine (5-FU or capecitabine) is not only the most widely used first-line treatment for metastatic colorectal cancer in the UK, but dominates combination chemotherapy used in this setting.

In recent years, there has been interest in improving clinical outcomes in metastatic colorectal cancer by the addition to chemotherapy of biological agents designed to specifically interact with the biological abnormalities that characterise tumours. Two such agents are approved by European regulators – cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR) and bevacizumab a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and disrupts the development and functioning of the tumour vasculature. Both of these drugs (cetuximab 2nd and subsequent lines and bevacizumab 1st line) have been reviewed by NICE in Technology Appraisal 118 (2007). This review rejected cetuximab because of concerns about both its clinical effectiveness and its cost-

effectiveness, whilst bevacizumab was accepted as being clinically effective but rejected on grounds of cost-effectiveness (ICER £62,857). More recently cetuximab has been recommended for restricted use, prior to surgery, in K-Ras wild-type patients with potentially resectable liver metastases (FAD for Single Technology Appraisal of cetuximab first-line in colorectal cancer, 2009). See later in this section for a brief discussion of hepatic resection.

The evidence for bevacizumab considered during TA118 derived from studies combining it with 5-FU+FA+/-irinotecan. At that time there was no information on the use of bevacizumab with capecitabine, rather than 5-FU and no Phase III data concerning oxaliplatin-based chemotherapy combined with bevacizumab.

Subsequently, the NO16966 trial filled these data gaps and supported extension of the Marketing Authorisation for bevacizumab to include combination with any fluoropyrimidine-based regimen. For practical purposes this means that capecitabine can now be used as an alternative to 5-FU as the fluoropyrimidine element of treatment and that oxaliplatin as well as irinotecan containing combination regimens can be used with bevacizumab.

Roche were requested to make a NICE submission based on these changes to the Marketing Authorisation and, as requested in the scope, will concentrate on the addition of bevacizumab to oxaliplatin based regimens. This is because:-

- It is what the scope demands
- Oxaliplatin regimens are most relevant to first-line treatment in the UK where they are the predominant treatment
- There is no substantial new evidence on the use of 5-FU+FA+/-irinotecan
- Roche have formulated a Patient Access Scheme, designed to ensure that bevacizumab can be added to the most widely used first-line chemotherapy regimens (FOLFOX and XELOX) whilst meeting NICE's criteria for cost-effectiveness

It should be noted that although a large and well-conducted randomized clinical trial (E3200) provides evidence for the clinical efficacy of bevacizumab added to second-line treatment with oxaliplatin-based chemotherapy, Roche is not proposing second-line use of bevacizumab plus oxaliplatin-based chemotherapy, because a preliminary analysis of cost-effectiveness indicates that second-line use of bevacizumab, at the dose tested in a randomised clinical trial (twice that proposed for first-line use) would not meet NICE's cost-effectiveness thresholds. Lack of second-line approval would be only a modest restriction on UK clinicians, who use oxaliplatin-based chemotherapy most widely in the first-line setting.

Resection of hepatic metastases

Metastatic colorectal cancer is, in most cases, considered to be incurable. However, in recent years an appreciation has developed that a minority of patients are diagnosed at a point where although their disease has spread from the bowel, the only discernable metastatic deposits are in the liver -typically the first site of disease spread. This has opened up the possibility of potentially curative metastatectomy for

such patients, provided their metastases are of a size and location that enables their excision whilst leaving behind a viable amount of healthy liver (reviewed in Nordlinger *et al* 2007) and without damaging other vital structures e.g. major blood vessels. In broad terms patients diagnosed with metastatic disease confined to the liver can be divided into three groups:-

- Those whose disease is never likely to be operable because of extent or position
- Those whose tumours are operable at the time of diagnosis
- Those whose tumours might be rendered resectable by a course of pre-operative chemotherapy to reduce their bulk.

As well as being a requirement prior to operating on the third group, there is a body of opinion that pre-operative chemotherapy may be useful in the second group with a view to shrinking the tumour making it more feasible and less traumatic to excise the entire tumour (see Nordlinger *et al.* 2007).

Randomised clinical trials in this area are limited and difficult for several reasons:-

- the current optimum chemotherapy is indicated for patients with liver metastases whether they are expected to undergo resection or not, making randomization between chemotherapy treatments problematic.
- there is no clear definition of what constitutes resectable and unresectable liver disease. Different studies report a very wide range of resection rates and it has been assumed that this is indicative of differences in criteria for resectability between centres and surgeons.
- Unresected liver metastases are likely to lead to death if left *in situ*, so that randomization between resection and systemic treatment only would be ethically unacceptable in patients where resection is possible. Overall, there is a widely held view that chemotherapy plus surgery is the way forward for improving survival in patients with initially unresectable liver metastases. NICE itself recognized as long ago as 2002 (Technology Appraisal 33) that new treatments for metastatic colorectal cancer (in this case oxaliplatin-based chemotherapy) could be justified on the basis that they allowed more patients to have their liver metastases surgically excised. This view was implicitly restated recently in the recent Final Appraisal Determination from the Health Technology Appraisal examining cetuximab in combination with chemotherapy for the first-line treatment for colorectal cancer (NICE 2009). This recommended the addition of cetuximab to chemotherapy only for K-ras wild-type tumours, in patients with unresectable metastatic disease restricted to the liver at the start of chemotherapy treatment and who are fit enough for resection following successful treatment. Therefore it is pertinent to consider data on the frequency and quality of liver resections amongst patients receiving any new systemic treatment regimen. Particularly one like bevacizumab which works equally well regardless of K-ras status.

4.2 What was the rationale for the development of the new technology?

The clinical rationale for developing better treatments for metastatic colorectal cancer is clear – the best current treatments delay disease progression for 8 or 9 months and extend patient survival by around 1 year.

From a scientific perspective, the rationale for the development of bevacizumab was provided by Folkman in 1971 who proposed that attacking the growth of the developing tumour vasculature (angiogenesis) would be a useful therapeutic strategy, because metastatic tumour deposits can grow to only a small size before they require their own blood supply to deliver oxygen and nutrients and remove waste products. Angiogenesis is a particularly attractive target because the process has little role in most normal adult tissues (the exceptions being areas of damage repair and the lining of the womb during the menstrual cycle) and because it involves an interaction with non-malignant vascular cells which are genetically much more stable than tumour cells, reducing the risk of drug resistance developing. After more than 30 years of intensive research into angiogenesis as a gateway to cancer treatment, bevacizumab became the first specific anti-angiogenic drug to receive regulatory approval, with an EMEA Marketing Authorisation for its use in colorectal cancer first granted on 12th January 2005

4.3 What is the principal mechanism of action of the technology?

Bevacizumab 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 *et al.* 2000).

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

In the UK, the current standard treatment for patients with metastatic colorectal cancer previously untreated for the condition is cytotoxic chemotherapy with a fluoropyrimidine (IV 5-FU potentiated with FA or oral capecitabine). For patients deemed fit enough, a second cytotoxic agent is added – usually, oxaliplatin (see Section 4.1) . It is proposed that bevacizumab should be added to oxaliplatin –based regimens (XELOX and FOLFOX) to improve their efficacy.

It should be noted that although addition of bevacizumab to other chemotherapy regimens (fluoropyrimidines alone or with irinotecan) is similarly beneficial in terms of clinical outcomes, these combinations have already been appraised by NICE and are outside the scope of this appraisal. See Section 2 for further background on this point.

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

As already discussed in Section 4.1, there is variation in the first-line chemotherapy used for patients with metastatic colorectal cancer in England and Wales. At first sight this appears to suggest a very large range of comparators for the bevacizumab plus oxaliplatin-based chemotherapy regimen in this appraisal. In practice, the following assumptions can be made:-

- Patients currently receiving first-line chemotherapy with a fluoropyrimidine alone (5-FU+FA or capecitabine monotherapy) receive this treatment because they are deemed unsuitable for more aggressive combination chemotherapy. Therefore, these patients are not eligible for oxaliplatin-based chemotherapy plus bevacizumab and are outside the scope of this appraisal. This point was discussed and agreed at the Scoping Meeting for this Appraisal.

- Patients currently receiving first-line chemotherapy with a fluoropyrimidine plus irinotecan will, usually, be receiving irinotecan rather than the dominant agent, oxaliplatin, because the latter is considered unsuitable (see section 4.1 for possible reasons). Therefore, patients receiving irinotecan-based first-line chemotherapy can, for the most part, be considered to be outside the scope of this appraisal (see Section 2 for more background on this point and how the request to use irinotecan-based chemotherapy as a comparator will be dealt with)

Therefore, this submission will concentrate, primarily, on the addition of bevacizumab to the oxaliplatin based regimens XELOX and FOLFOX.

4.6 Provide details of any relevant guidelines or protocols.

NICE itself has issued a number of **Technology Appraisals** relating to the drug treatment of colorectal cancer. These have shaped the current treatment pathway followed by patients with metastatic colorectal cancer being treated by the NHS. These are listed in chronological order:-

May 2003 TA61. Recommended oral treatment with capecitabine or tegafur-uracil plus FA as first-line treatment options for patients with metastatic colorectal cancer against the then current standard of IV 5-FU plus FA.

August 2005 TA93. Recommended irinotecan or oxaliplatin in combination with 5-FU plus FA as options for the first-line treatment of metastatic colorectal cancer against the then current standard of IV 5-FU plus FA (plus oxaliplatin in patients with liver metastases that would potentially become resectable after effective chemotherapy). TA93 further recommended oxaliplatin plus 5-FU+ FA or irinotecan monotherapy as second- or subsequent-line treatment against the then standard of irinotecan monotherapy. Resulted in patients fit enough for two lines of aggressive chemotherapy receiving both irinotecan (+/- 5-FU+FA) and oxaliplatin plus 5-FU+ FA in sequence. In clinical practice oxaliplatin plus 5-FU+FA became the preferred first-line treatment with irinotecan reserved for later use, presumably because of its greater toxicity (see Section 4.1 for discussion of this issue).

April 2006 TA100. Recommended oral capecitabine or IV oxaliplatin plus 5-FU+FA as options for the post-surgical adjuvant treatment of resected Dukes' Stage C (Stage III) colorectal cancer against the then current standard of IV 5-FU+FA for patients unsuitable for oxaliplatin or irinotecan containing combinations. Resulted in many fitter patients presenting with operable disease receiving oxaliplatin in the adjuvant setting making them unsuitable for this agent for this first-line treatment of metastatic disease if progressing on or shortly after completion of adjuvant treatment.

June 2007 TA118. Recommended that bevacizumab should not be added to first-line chemotherapy of metastatic colorectal cancer with 5-FU plus FA+/- irinotecan, because of concerns about cost-effectiveness. It also recommended that cetuximab should not be used with irinotecan as a second- or subsequent-line treatment for metastatic colorectal cancer because of concerns about both clinical and cost-effectiveness. This guidance resulted in UK clinicians being unable to utilize two biological agents which now form part of the standard treatment package in most European countries, the USA and elsewhere.

June 2008 TA130. Appraisal of the place of cetuximab after the failure of the first-line treatment with oxaliplatin-based therapy for metastatic colorectal cancer abandoned after failure of manufacturer to submit evidence. Resulted, by default, in negative guidance for cetuximab in this situation.

June 2009 A Final Appraisal Determination (FAD) is produced allowing the option of adding cetuximab to first-line chemotherapy with FOLFOX or FOLFIRI under very restricted circumstances – essentially to facilitate resection of hepatic metastases in patients whose primary tumour has been successfully removed and whose metastatic disease is confined to the liver. This guidance is likely to result in increased use of cetuximab in patients whose tumours have wild-type *RAS* genes but not those with activating *KRAS* mutations, where the available evidence suggests that cetuximab has little benefit.

In addition NICE has published a revised version of the Cancer Service Guideline *"Improving Outcomes in Colorectal Cancer"*. This was first published by the Department of Health in 1997 and the revised version in 2004. Since it now predates all but one of the above Technology Appraisals, its relevance to the current drug treatment of metastatic colorectal cancer is very limited and the new clinical guideline due in 2011 is awaited with interest.

Many other countries have guidelines covering this therapeutic area.

For example, in the USA, the National Comprehensive Cancer Center Network (NCCN) issues "*Practice Guidelines in Oncology*" outlining acceptable standard treatment that patients can expect to receive. In its 2009 edition it recommends that XELOX (CapOx in its terminology) plus bevacizumab or FOLFOX plus bevacizumab should be available as first-line treatment options. In Europe, the current "*Clinical Recommendations for the Treatment of Advanced Colorectal Cancer"* from the European Society for Medical Oncology note the improvement in outcomes that can be achieved by the addition of bevacizumab to first-line chemotherapy with both oxaliplatin- and irinotecan-based regimens and recommend that the addition of bevacizumab to such chemotherapy should be considered (Van Cutsem *et al.* 2008).

5 Equity and equality

The Institute considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in population groups, evidence on differential treatment effects in population groups, and epidemiological evidence on risks or incidence of the condition in population groups. Evidence submitters are asked to consider whether the chosen decision problem could be impacted by the Institute's responsibility in this respect; including in considering subgroups and access to recommendations that use a clinical or biological criterion.

5.1 Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None identified

How has the analysis addressed these issues?

Not applicable

6 Clinical evidence

6.1 ***Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUORUM statement checklist (www.consort-statement.org/QUOROM.pdf).***

6.2 ***The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.***

6.3 ***The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used Formal assessments of heterogeneity should be included.***

6.4 ***In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation***

inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented.

6.5 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Literature searching was conducted by a member of the Roche Medicines Information team experienced in electronic database interrogation and familiar with bevacizumab. The following databases were searched: BIOSIS Previews, EMBASE, MEDLINE, EMBASE last 8 weeks and MEDLINE in process. The *Journal of Clinical Oncology* electronic archive was also searched for abstracts presented at meetings of the *American Society of Clinical Oncology* (ASCO). ASCO is the leading global oncology conference and it is unusual for any significant clinical trial not to be presented here (often the first presentation).

Search strategies used were as follows:-

Search strategy for BIOSIS Previews covering search period 1993-1st May 2009

No.	Database	Search term	Info added since	Results
1	BIYY	bevacizumab	unrestricted	1559
2	BIYY	colorectal ADJ cancer	unrestricted	29605
3	BIYY	oxaliplatin	unrestricted	2410
4	BIYY	1 AND 2 AND 3	unrestricted	90
5	BIYY	4 AND PT=LITERATURE-REVIEW	unrestricted	28
6	BIYY	4 NOT 5	unrestricted	62

Search strategy for EMBASE and MEDLINE 1993-1st May 2009

No.	Database	Search term	Info added since	Results
1	EMYY	Bevacizumab.W..MJ.	unrestricted	1577
2	EMYY	Colorectal-Cancer.MJ.	unrestricted	21426
3	EMYY	Oxaliplatin.W..MJ.	unrestricted	1913
4	EMYY	1 AND 2 AND 3	unrestricted	52
5	EMYY	4 AND CLINICAL-TRIAL#	unrestricted	33
6	MEYY	monoclonal ADJ antibodies	unrestricted	81020
7	MEYY	6 AND bevacizumab	unrestricted	508
8	MEYY	Colorectal-Neoplasms.MJ.	unrestricted	27305
9	MEYY	Drug-Therapy.MJ.	unrestricted	499922
10	MEYY	7 AND 8 AND 9	unrestricted	109
11	MEYY	10 AND PT=CLINICAL-TRIAL#	unrestricted	10
12	MEYY	10 AND REVIEW=YES	unrestricted	76
13	MEYY	11 NOT 12	unrestricted	10
14	EMYY MEYY	combined sets 5, 13	unrestricted	43
15	EMYY MEYY	dropped duplicates from 14	unrestricted	0
16	EMYY MEYY	unique records from 14	unrestricted	43

Search strategy for EMBASE last 8 weeks and MEDLINE in process search conducted on 1st May 2009

No.	Database	Search term	Info added since	Results
1	EMBA	bevacizumab	unrestricted	143
2	EMBA	colorectal ADJ cancer	unrestricted	613
3	EMBA	1 AND 2	unrestricted	24
4	MEIP	bevacizumab	unrestricted	300
5	MEIP	colorectal ADJ cancer	unrestricted	1168
6	MEIP	4 AND 5	unrestricted	42
7	MEIP	6 AND REVIEW=YES	unrestricted	0
8	EMBA MEIP	combined sets 3, 6	unrestricted	66
9	EMBA MEIP	dropped duplicates from 8	unrestricted	12
10	EMBA MEIP	unique records from 8	unrestricted	54

Search strategy for Journal of Clinical Oncology Archive search for ASCO abstracts covering search period Jan 2000-1st May 2009

Bevacizumab – required in abstract title

Colorectal OR randomised OR randomized required in title or abstract text

In addition, the EMEA Regulatory Submission that resulted in approval of bevacizumab for use in addition with oxaliplatin based chemotherapy was reviewed for further relevant studies that would have had to be declared at the point of submission. The bevacizumab Product Medical Manager for gastro-intestinal indications and relevant Medicines Information Product Specialist at Roche UK, both of whom review bevacizumab data on an ongoing basis, were asked for any further relevant studies of which they were aware.

6.6 Study selection

6.6.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Table 2 gives the number of records obtained from each of the above sources during searching and the number excluded as not giving information on a randomised trial of the intervention under review in the setting under review and Table 3 groups retained records according to the study to which they refer.:

Table 4 Records from literature searches identified, rejected and retained as representing an RCT including the intervention of interest for this appraisal

Source	Records found	Excluded based on title	Excluded based on abstract	Excluded based on full text	Total excluded	Records retained
BIOSYS	62	15	24	21	60	2
EMBASE/MEDLINE 1993>Present	43	3	26	7	36	7
EMBASE last 8 weeks/MEDLINE in process	50	7	43	0	50	4
ASCO abstracts	190	0	176	Not applicable	176	14
Avastin regulatory submission EU/1/04/300/001	3 RCTs discussed	0	0	0	0	3 RCTs

Personal knowledge of Roche Medicines Information expert*	1	0	0	0	0	1

Total records retained as referring to RCTs including the intervention of interest 31

*One publication relating to the E3200 study was not identified by other search techniques. This appears to be anomalous result rather than the result of an inadequate search strategy – the search identified other publications relating to this study and other publications from the journal in question.

Table 5: Retained records (n=31) from literature search grouped according to the randomised clinical trial (RCT) to which they refer. Left-hand column represents the complete RCT list.

Trial	Pertinent records (numbers and description)
E3200	1. Giantonio BJ *et al* High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. *J Clin Oncol.* 2005; **23** (16S): Abstr 2. 2. Giantonio BJ *et al* Impact of bevacizumab dose reduction on clinical outcomes for patients treated on the Eastern Cooperative Oncology Group's Study E3200. *J Clin Oncol.* 2006; **24** (18S): Abstr 3538. 3. Catalano PJ *et al.* Outcome differences for African Americans and Caucasians treated with bevacizumab, FOLFOX4 or the combination in patients with metastatic colorectal cancer (MCRC): Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol.* 2007; **25**(18S): Abstr 4100 4. Giantonio BJ *et al*. Magnitude of progression-free survival (PFS) improvement and treatment (Tx) duration in metastatic colorectal cancer (MCRC) for bevacizumab (BV) in combination with oxaliplatin-containing regimens: An analysis of two phase III studies. *J Clin Oncol.* 2007; **25** (18S): Abstr 4073. 5. Cohen MH *et al*. FDA drug approval summary: bevacizumab plus FOLFOX4 as second-line treatment of colorectal cancer. *Oncologist.* 2007; **12**: 356-361 5. Giantonio BJ *et al.* Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group study E3200. *J Clin Oncol.* 2007; **25**: 1539-1544. 6. Avastin regulatory submission EU/1/04/300/001

NO16966 (also known as XELOX-1)

7. Saltz L *et al*. Bevacizumab (Bev) in combination with XELOX or FOLFOX4: Updated efficacy results from XELOX-1/NO16966, a randomized phase III trial in first-line metastatic colorectal cancer *J Clin Oncol.* 2007; **25** (18S): Abstr 4028. 8. Cassidy J *et al.* Surgery with curative intent in patients (pts) treated with first-line chemotherapy (CT) + bevacizumab (BEV) for metastatic colorectal cancer (mCRC): First BEAT and NO16966. *J Clin Oncol.* 2008; **26**(15S): Abstr 4073.

4. Giantonio BJ *et al*. 2007 (record 4 above refers also to this trial)

9. Saltz LB *et al.* Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol.* 2008; **26**: 2013-2019.

10. Preeta T and Grothey A. FDA drug approval summary: Bevacizumab plus FOLFOX as second-line treatment of colorectal cancer. *Oncologist.* 2007; **12**: 356-361.

11. Avastin regulatory submission EU/1/04/300/001 including 4-months Safety Update Report 1026598

TREE 2

12. Hochster H *et al.* Safety, tolerability and efficacy of the addition of bevacizumab to oxaliplatin/fluoropyrimidine regimens as first-line treatment of metastatic colorectal cancer (mCRC): Results of TREE 2 cohort of the TREE study. *EJC Supplements.* 2005; **3**: 173.

13. Hochster HS *et al.* Safety and efficacy of oxaliplatin/fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer (mCRC): Final analysis of the TREE-Study. *J Clin Oncol.* 2006; **24**(18S): Abstr 3510.

14. Hochster HS *et al*. Safety and efficacy of bevacizumab (Bev) when added to oxaliplatin/fluoropyrimidine (O/F) regimens as first-line treatment of metastatic colorectal cancer (mCRC): TREE 1 & 2 studies. *J Clin Oncol.* 2008; **23**(16S): Abstr 3515.

15. Hochster HS *et al.* Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE study. *J Clin Oncol.* 2008; **26**: 3523-3529.

16. Avastin regulatory submission EU/1/04/300/001

AIO 0604

17. Schmiegel WH *et al.* Comparable safety and response rate with bevacizumab in combination with capecitabine/oxaliplatin (CapOx/Bev) versus capecitabine/irinotecan (CapIri/Bev) in advanced CRC (mCRC): A randomized phase II study of the AIO GI tumor study group. *J Clin Oncol.* 2007; **25**(18S): Abstr 4034.

18. Reinacher-Schick AC *et al.* Activity of the combination of bevacizumab (Bev) with capecitabine/irinotecan (CapIri/Bev) or capecitabine/oxaliplatin (CapOx/Bev) in advanced colorectal cancer (ACRC): A randomized phase II study of the AIO Colorectal Study Group (AIO trial 0604) *J Clin Oncol.* 2008; **26**(15S): Abstr 4030

DREAM-OPTIMOX

19. Tournigand C *et al.* Modified (m)Folfox7/bevacizumab (B) or modified (m)Xelox/bevacizumab with or without erlotinib (E) in first-line metastatic colorectal cancer (MCRC): Results of the feasibility phase of the DREAM-OPTIMOX3 study (GERCOR). *J Clin Oncol.* 2007; **25**(18S): Abstr 4097.

CAIRO2

20. Pander J *et al.* Pharmacogenetic (PGx) analysis of toxicity after oxaliplatin (Ox), capecitabine (Cap), bevacizumab (Bev) and cetuximab (cet) therapy for advanced colorectal cancer (ACC): First resultsfrom the Dutch Colorectal Cancer Group (DCCG)-CAIRO2 trial. *J Clin Oncol.* 2008; **26**(15S): Abstr 2574

21. Punt CJ *et al.* Randomized phase III study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). *J Clin Oncol.* 2008; **26**(15S): Abstr LBA 4011.

22. Punt CJA *et al.* A randomised phase III study on capecitabine, oxaliplatin and bevacizumab with or without cetuximab in first-line advanced colorectal cancer, the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim analysis of toxicity. *Annals Oncol.* 2008; **19**: 734-738.

23. Tol J *et al.* Randomised phase III study of capecitabine, oxaliplatin and bevacizumab (CAPOX-B) with or without cetuximab in advanced colorectal cancer (ACC), the CAIRO2 study of the Dutch Colorectal Cancer Group (DCCG). An interim safety analysis. *EJC Supplements.* 2007; **5**: 234-235.

24. Tol, J *et al.* Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *New Engl J Med.* 2009; 360: 563-572.

Cediranib versus bevacizumab Phase II

25. Cunningham D *et al.* A phase II, double-blind, randomized multicenter study of cediranib with FOLFOX in patients with previously treated metastatic colorectal cancer (mCRC): Final PFS results. *J Clin Oncol.* 2008a; **26**(15S): Abstr 4028.

HORIZON III

26. Robertson JD *et al.* Phase III trial of FOLFOX plus bevacizumab (AZD2171) as first-line treatment of patients with metastatic colorectal cancer: HORIZON III. *Clin Colorectal Cancer.* 2009; **8**: 59-60

NCT00625651

27. Fuchs CS and Saltz LB. Evaluating the addition of AMG 655 to mFOLFOX6/bevacizumab in metastatic colorectal cancer. *Community Oncol.* 2008; **5**: 1-4.

B-FOLFOX+/-panitumab	28 & 29. Giusti RM *et al* FDA review of a panitumumab (Vectibix TM) clinical trial for first-line treatment of metastatic colorectal cancer. *Oncologist.* 2009; **14**: 284-290. (Record found twice)
	30. Hecht RJ *et al.* A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol.* 2009; **27**: 672-680.

6.6.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

The following criteria were applied to the trials listed in Section 6.2.1:-

1. There should be a non-bevacizumab arm. Without this it is impossible to determine the benefit of bevacizumab, a key issue in this appraisal.

2. There should be an arm without any experimental antiangiogenic drug. Studies comparing bevacizumab with other experimental anti-angiogenic agents (e.g. cediranib) are uninformative with regard to the question under consideration – what does bevacizumab add to oxaliplatin-based chemotherapy used alone?

6.6.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The impact of applying the rules described in Section 6.2.2 to the trials identified in Section 6.2.1 is shown in Table 6.

Table 6: Reasons for exclusion/inclusion of randomised clinical trials of oxalipatin-based chemotherapy plus bevacizumab identified during literature searching in the clinical section of this appraisal

Study	Include/exclude?	Reasons for exclusion
E3200	Include	
NO16966	Include	
TREE2	Exclude, but consideration of the TREE1 and TREE2 studies included in the non-randomised trial section of this submission (see Section 6.2.4)	No non-bevacizumab containing arm – 3 different bevacizumab+oxaliplatin+5-FU+FA study arms (Rule 1). But TREE1 and TREE2 represent sequential cohort studies of a relevant patient group and are included in the non-randomised trial section of this submission
AIO0604	Exclude	No non-bevacizumab arm (Rule 1).
DREAM-OPTIMOX	Exclude	No non-bevacizumab arm (Rule 1).
CAIRO2	Exclude	No non-bevacizumab arm (Rule 1).
Cediranib versus bevacizumab Phase II	Exclude	No arm without anti-angiogenic agent (Rule 2)
HORIZON III	Exclude	No arm without anti-angiogenic agent (Rule 2)
NCT00625651	Exclude	No non-bevacizumab arm (Rule 1)
B-FOLFOX+/-panitumab	Exclude	No non-bevacizumab arm (Rule 1)

6.6.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

The TREE (Three Regimens of Eloxatin Evaluation) study was originally designed as a randomised comparison of the tolerability of three different combination regimens of oxaliplatin and a fluoropyrimidine used for the first-line chemotherapy of metastatic colorectal cancer (the TREE-1 cohort). It opened for recruitment in November 2002. As recruitment neared completion evidence was emerging of the value of adding bevacizumab to combination chemotherapy for metastatic colorectal cancer and a protocol amendment was made. This allowed for the recruitment of a further cohort (the TREE-2 cohort) randomised between the same three chemotherapy regimens with the addition of bevacizumab administered at a dose of 5 mg/kg IV every two weeks to all regimens. Recruitment to the TREE-1 cohort was closed in November 2003 when 50 patients had been recruited to each arm and between November 2003 and April 2004 223 patients were recruited into the TREE-2 cohort. Thus, although TREE does not include randomisation between chemotherapy alone or with bevacizumab it does provide evidence of the efficacy of oxaliplatin-based

chemotherapy with and without bevacizumab in two very similar cohorts of patients treated, largely, in the same centres and recruited over a relatively short period of time. As such the TREE studies provide useful supportive information in this appraisal.

6.6.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

No relevant studies known. The role of bevacizumab combined with oxaliplatin-based (and other chemotherapy regimens) is now so well established that it is unlikely that further major studies addressing the question of its efficacy will be conducted. However, oxaliplatin-based chemotherapy plus bevacizumab is increasingly being used as the control arm in clinical studies assessing the efficacy of novel agents including experimental angiogenics.

6.7 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

6.7.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

6.7.1.1 Overview of RCT evidence supporting this submission

NO16966 Study

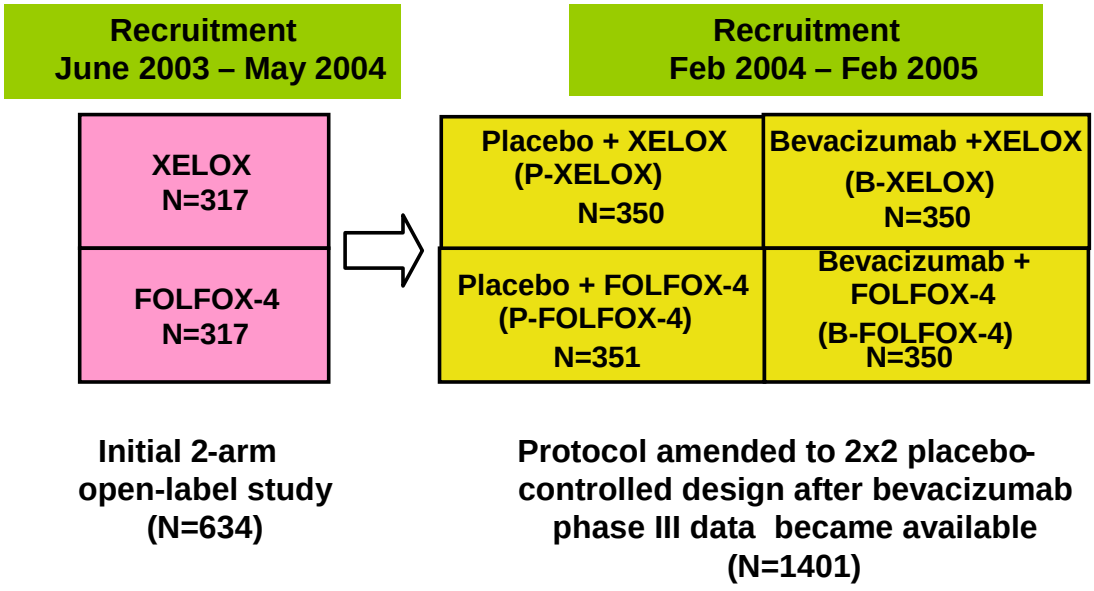
This submission is based primarily on the NO16966 study which formed the basis of the regulatory submission to the EMEA which resulted in the extension to the Marketing Authorisation for Avastin that precipitated this Appraisal. This study began as a 2-arm investigation into whether the IV 5-FU and FA elements of the FOLFOX-4 regimen for the first-line treatment of metastatic colorectal cancer could be replaced by oral capecitabine (as part of a XELOX regimen), without prejudicing antitumour efficacy, defined as non-inferiority of progression-free survival (PFS). However, soon after the commencement of enrolment into NO16966, results were presented from studies demonstrating the benefit of adding bevacizumab to chemotherapy regimens

incorporating 5-FU plus FA+/-irinotecan (Hurwitz *et al.* 2004; Kabbinavar *et al.* 2003; 2005 a, b).

It became apparent that any first-line study not including bevacizumab would be irrelevant to clinical practice in many parts of the world by the time it completed. Additionally, a requirement emerged for information on the impact of adding bevacizumab to oxaliplatin-containing chemotherapy. For these reasons, after randomisation of the first 634 patients to XELOX or FOLFOX, the protocol for NO16966 was amended to incorporate a double randomisation in which patients were subsequently randomised to XELOX or FOLFOX plus bevacizumab or placebo as shown in Figure 4.

The co-primary study end-points after protocol modification were, firstly, superiority of PFS (assessed on an intent-to-treat [ITT] basis) in patients receiving chemotherapy (XELOX or FOLFOX) plus bevacizumab *versus* those receiving chemotherapy alone. The second-co-primary endpoint was non-inferiority of PFS in the population receiving XELOX (with or without bevacizumab or placebo) *versus* those receiving FOLFOX (with or without bevacizumab). The NO16966 study met both of its co-primary endpoints thus providing information on two novel bevacizumab combinations (B-XELOX and B-FOLFOX) with greater activity than the FOLFOX regimen which represents the dominant first-line treatment for metastatic colorectal cancer in England and Wales.

Figure 4: Design of the NO16966 study

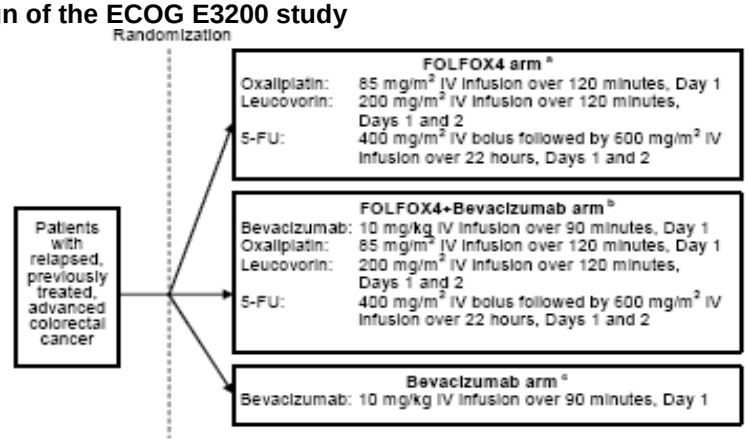


ECOG 3200 Study

This study, which supports the clinical benefit of adding bevacizumab to chemotherapy with an oxaliplatin+fluoropyrimidine combination, was conducted by the Eastern Collaborative Oncology Group in the USA. It started as a three arm study comparing bevacizumab alone with FOLFOX-4 chemotherapy alone and the

combination of bevacizumab and FOLFOX-4 in patients with relapsed, previously treated advanced colorectal cancer. The plan was to recruit 293 patients per arm.

Figure 5: Design of the ECOG E3200 study



5-FU = 5-fluorouracil; IV = intravenous.
Note: Protocol Therapies were to be administered every 2 weeks. Oxaliplatin and leucovorin could be administered simultaneously. Dose calculations were based on actual body weight at the beginning of each cycle.
[a] Referred to in the protocol as Arm B.
[b] Referred to in the protocol as Arm A.
[c] Referred to in the protocol as Arm C.

The dose of bevacizumab used in this study was 10 mg/kg every 2 weeks. At the time of study initiation phase II data indicated that both 5 mg/kg and 10 mg/kg delivered every two weeks were tolerable and active dose schedules, but clear evidence of the relative risk:benefit ratios of these two doses was unavailable (this predated the availability of Phase III data showing the efficacy of the lower dose). Therefore, the ECOG investigators selected the higher dose based on a desire to increase the likelihood of benefit in the pre-treated and advanced patient population to be enrolled, whom it was assumed would be relatively resistant to further therapy.

On March 11 2003, prior to the first formal interim efficacy analysis, the bevacizumab monotherapy arm was closed to further enrolment based on a review of early results by the ECOG data monitoring committee, with enrolment continuing on a 1:1 basis in the two remaining treatment arms.

The primary efficacy end-point for this study was improved duration of survival defined as time from randomistion to death from any cause. The study met this primary end-point with stratified analysis demonstrating that the addition of bevacizumab resulted in significantly longer survival for patients with receiving B-FOLFOX than those receiving FOLFOX chemotherapy alone.

6.7.1.2 Study NO16966: Design and execution

Study design

NO16966 was a multicentre, multinational, randomized 2-part study (as described above and illustrated in Figure 4.). In the initial 2-arm part, patients were randomised to receive either XELOX or FOLFOX-4. In the 2 x 2 factorial part, patients were randomized to receive either placebo (P) plus XELOX (P-XELOX), bevacizumab (B) plus XELOX (B-XELOX), P-FOLFOX-4 or B-FOLFOX-4. Although study participants

were blinded to the allocation of bevacizumab and its placebo, it was not appropriate to blind them to the chemotherapy allocation, since this would have subjected patients allocated to XELOX to the unnecessary insertion of a permanent venous access device and 48 hours of IV infusion with placebo 5-FU every fortnight.

Randomisation

Patients were assigned to a treatment group via the process of adaptive randomisation, with stratification. Randomisation numbers and treatment allocation were assigned by central randomisation. During both the initial two-arm and subsequent four-arm parts of the study there was an equal chance of randomisation to any study arm. Throughout the study randomisation was stratified to ensure study arms were balanced with respect to the following prognostic factors: ECOG Performance Status (0 *versus* 1), number of metastatic sites (organs) at baseline (1 *versus* >1), alkaline phosphatase level at baseline (within normal range *versus* above normal range), liver as a site of metastasis (yes *versus* no), and geographic region. The same weight was assigned to all these factors. Stratification by these factors was accomplished by dynamic randomisation using an interactive voice response service (IVRS).

A list of patient randomisation numbers and associated treatment(s) was generated by Roche. The randomisation number, the treatment group allocation/medication numbers were provided to the investigator via the IVRS over the telephone at the time of enrollment. In addition, a confirmation fax containing the randomisation number and medication kits assigned to a patient was sent from the IVRS to the investigator.

Recruitment

A total of 2,035 patients were randomised (634 to the initial comparison of XELOX and FOLFOX and 1401 to the 2 x 2 randomisation to XELOX or FOLFOX +/- bevacizumab), including one patient who was randomised twice in error (B-FOLFOX, no treatment received and P-XELOX, treatment received). A total of 2,034 patients received treatment. Patients were recruited by 216 investigators (including one of the two Principal Investigators, Prof James Cassidy from the Beatson Oncology Centre in Glasgow) in 32 countries including the UK. The first patient was randomised on 15th July 2003 and the last on February 10th 2005. The data-base was locked for final analysis on January 31st 2006. A further analysis (which forms the basis of this submission was carried out with a data cut-off of 31st January 2007)

Study treatments

The treatment regimens of relevance to this specific decision problem from the NO16966 study were as follows:-

B-FOLFOX(14 day cycle)

Day 1

Oxaliplatin 85 mg/mg^2 IV infusion over 2 hours plus FA, 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours, plus bevacizumab 5 mg/kg as IV infusion over 30-90 minutes prior to oxaliplatin on Day 1.

Day 2

FA 200 mg/m^2 IV infusion over 2 hours, followed by 5-FU 400 mg/m^2 as IV bolus injection followed by 5-FU 600 mg/m^2 IV infusion over 22 hours

P-FOLFOX (14 day cycle)

As B-FOLFOX but with placebo identical in appearance to bevacizumab 5mg/kg administered on Day 1 in place of bevacizumab

FOLFOX (14 day cycle)

As B-FOLFOX but without bevacizumab or placebo on Day 1

B- XELOX (21 day cycle)

Day 1

Bevacizumab 7.5 mg/kg IV over 30-90 minutes plus oxaliplatin 130 mg/mg^2 IV infusion over 2 hours

Days 1-14

Capecitabine 1000 mg/m^2 by mouth, twice daily, within 30 minutes of the end of breakfast and dinner.

P- XELOX (21 day cycle)

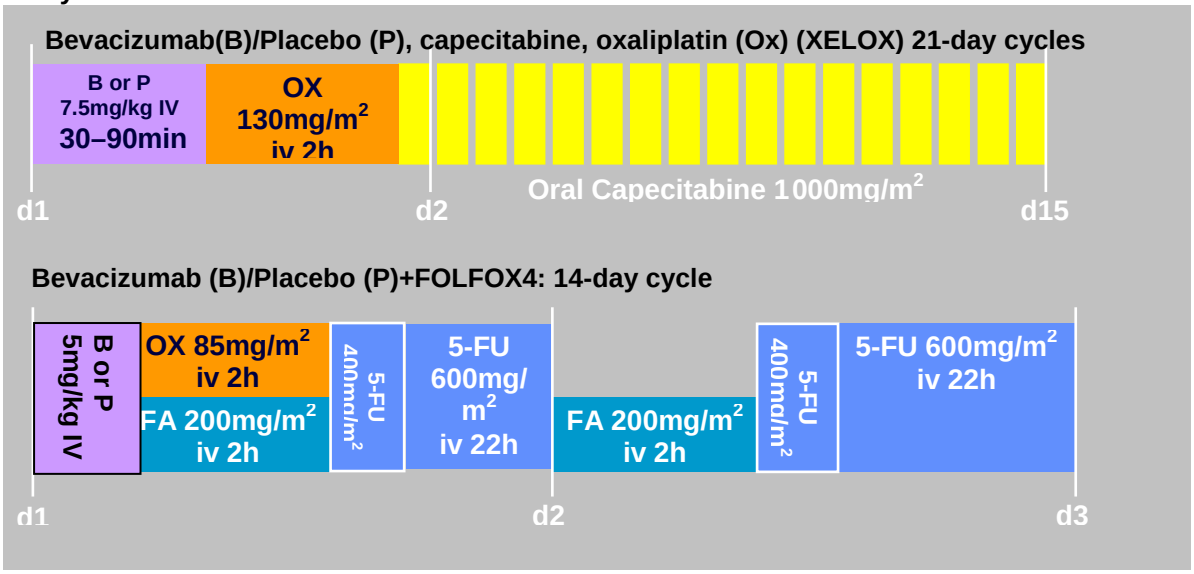
As B-XELOX but with placebo identical in appearance to bevacizumab 7.5 mg/kg IV over 30-90 minutes on Day 1 in place of bevacizumab

XELOX

As B-XELOX but with neither bevacizumab or placebo on Day 1

The dosing schedules for the B-XELOX and FOLFOX-4 regimens are illustrated schematically in Figure 3.

Figure 6: Dosing schedules for B/P-XELOX and B/P-FOLFOX-4 as used in the NO16966 study



Abbreviations: FA, folinic acid.

The different doses of bevacizumab and oxaliplatin when comparing the B-XELOX and B-FOLFOX arms of the NO16966 study ensured that the same dose intensity of these drugs was achieved with 2-weekly and 3-weekly regimens and the same total dose during the 48 week primary treatment phase of the study.

Treatment duration

All patients were scheduled to receive at least 48 weeks of treatment with one of the above regimens, unless they experienced one of the following:-

- progression of disease
- unacceptable toxicity
- tumour shrinkage that permitted resection of a previously inoperable tumour.

In the event of unacceptable toxicity attributable to the oxaliplatin, fluoropyrimidine or bevacizumab/placebo components of treatment, then oxaliplatin, all cytotoxic drugs or bevacizumab/placebo could be discontinued, respectively (oxaliplatin could not be continued in the absence of a fluoropyrimidine).

Patients still on treatment at the end of the 48 week “Primary Study Treatment Phase” were eligible to continue on their allocated treatment until disease progression at the discretion of the investigator. Patients could remain on treatment as part of this post-study treatment phase until disease progression. All patients stopping treatment were followed up for PD (if it had not occurred at the time of

treatment cessation) and all were followed up for survival. Assessment schedules are shown in Table 7.

Table 7: Schedule of treatment and tumour assessment in study NO16966

Phase	Screen/baseline	Primary Study Treatment Phase	Post-study Treatment Phase (optional)	Follow-up phase
Duration	Day -21 to 0	Day 1, Week 1 to Week 48	Until PD	Until death
Study treatment	None	Yes until PD or unacceptable toxicity	Optional, until PD	None
Assessment (all responses assessed according to RECIST criteria)	Scans </= 21 days	Scans every 6 weeks (plus confirmation>28 days for response)	Scans every 6 weeks until week 60, then every 3 months	Scans every 6 weeks until week 60, then every 3 months for patients without PD. Survival every 3 months

Abbreviations: PD, Progressive Disease

6.7.1.3 ECOG Study E3200 Design and execution

Study design

E3200 was a Phase III, randomized, controlled trial conducted at 220 study sites in the USA that recruited 829 patients who had failed treatment with irinotecan and 5-FU administered separately or together for metastatic colorectal cancer. It was designed was designed to compare the benefit of bevacizumab used alone or added to FOLFOX-4 chemotherapy for the treatment of relapsed disease.

Randomisation

Randomisation was carried out centrally by the ECOG Co-ordinating Center. Patients were randomised to the three treatment arms on a 1:1:1 basis, stratified by

ECOG performance status (0 *versus* >/=1) and prior radiation therapy (yes *versus* no) with the bevacizumab alone arm closed early subsequent to a review of efficacy by the data monitoring committee. After closure of the bevacizumab alone arm randomization continued on a 1:1 basis to the other two arms.

Recruitment

A total of 829 patients were recruited (292 to FOLFOX; 293 to B-FOLFOX and 244 to B alone). Patients were randomised between November 2001 and April 2003 with accrual to the B alone arm closed in March 2003.

Study Treatments

These are described in Figure 2. FOLFOX-4 is the same as has already been described for the NO16966 study. B-FOLFOX was also as described for the NO16966 study except that the bevacizumab dose was doubled to 10 mg/kg with each cycle and the B alone arm consisted of bevacizumab 10mg/kg infused over 30-90 minutes every 2 weeks.

Treatment was continued until disease progression or unacceptable toxicity, except in patients who achieved a complete response (CR) and completed up to two additional cycles of treatment or who, after achieving a partial response (PR), had all remaining disease surgically resected . There was no maximum duration of treatment.

6.7.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

6.7.2.1 Study population for NO16966

The main criteria for study entry were that patients should be, >/= 18 years of age and have a histologically confirmed diagnosis of adenocarcinoma of the colon or rectum with metastatic disease. Detailed entry criteria are as follows:-

Inclusion Criteria

• Male or female outpatients aged ≥ 18 years

• Be ambulatory and have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
• Have histologically confirmed adenocarcinoma of the colon or rectum with metastatic disease
• Have at least one unidimensionally measurable lesion with a diameter >20 mm using
conventional computed tomography (CT) or magnetic resonance imaging (MRI) scans or >10 mm using spiral CT scans
• Have a life expectancy of at least 3 months
• Be willing and able to comply with the protocol for the duration of the study
• Give written informed consent prior to study-specific screening procedures, with the
understanding that the patient could withdraw from the study at any time, without prejudice

Exclusion Criteria

• Pregnant or lactating women
• Women of childbearing potential with either a positive or no pregnancy test at baseline. Postmenopausal women must have been amenorrheic for at least 12 months to be considered of non-childbearing potential

• Sexually active males and females (of childbearing potential) unwilling to practice contraception during the study

• Prior treatment with oxaliplatin

• Prior treatment with bevacizumab

• Prior systemic therapy (for instance, cytotoxic chemotherapy or ctive/passive immunotherapy) for advanced or metastatic disease

  - Adjuvant or neo-adjuvant treatment for non-metastatic (M0) disease was allowed if completed at least 6 months prior to initiation of study treatment

  - If prior adjuvant therapy was received, patients must not have progressed during therapy or within 6 months of therapy completion

  - Prior radiotherapy was permitted if it was not administered to target lesions selected for this study, unless progression of the selected target lesions within the radiation portal is documented, and provided that, if administered for lesions other than bone metastases, it was completed at least 4 weeks before randomisation

  - Prior surgical treatment of Stage IV disease was permitted.

- History of another malignancy within the last five years except cured basal cell carcinoma of skin and cured carcinoma *in-situ* of uterine cervix

- Evidence of clinically detectable ascites at study treatment start (*e.g.*, did not include ascites as radiological finding only)

- History or evidence upon physical examination of CNS disease (*e.g.*, primary brain tumor, seizure not controlled with standard medical therapy, or any brain metastases).

- History of psychiatric disability judged by the investigator to be clinically significant, precluding informed consent or interfering with compliance for oral drug intake

- Clinically significant (*i.e.*, active) cardiovascular disease *e.g.*, uncontrolled hypertension, unstable angina, New York Heart Association (NYHA) grade II or greater congestive heart failure, serious cardiac arrhythmia requiring medication, or grade II or greater peripheral vascular disease. In addition patients with myocardial infarction or cerebrovascular accident within 1 year prior to study treatment start were excluded

- Lack of physical integrity of the upper gastrointestinal tract, malabsorption syndrome, or inability to take oral medication.

- Interstitial pneumonia or extensive symptomatic fibrosis of the lungs

- Known peripheral neuropathy ≥ NCI CTCAE grade 1. Absence of deep tendon reflexes as the sole neurologic abnormality did not render the patient ineligible

- Organ allografts requiring immunosuppressive therapy

- Serious, non-healing wound, ulcer, or bone fracture

- Evidence of bleeding diathesis or coagulopathy

- Serious uncontrolled intercurrent infections, or other serious uncontrolled concomitant disease

- Moderate or severe renal impairment: creatinine clearance equal to or below 50 mL/min (calculated according to Cockroft and Gault), or serum creatinine > 1.5 x upper limit of normal (ULN).

- Proteinuria at baseline: Patients with ≥ 1+ baseline proteinuria on dipstick test, underwent a 24 –hour urine collection and had to have <500mg of urinary protein/24hr

- Any of the following laboratory values:

- Absolute neutrophil count (ANC) < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Hemoglobin < 9 g/dL (may be transfused to maintain or exceed this level)
- International Normalized Ratio (INR) > 1.5
- Total bilirubin > 1.5 x upper limit of normal (ULN)
- ALAT, ASAT > 2.5 x ULN, or > 5 x ULN in case of liver metastases
- Alkaline phosphatase > 2.5 x ULN, or > 5 x ULN in case of liver metastases, or >10 x ULN in case of bone metastases.

• Prior unanticipated severe reaction to fluoropyrimidine therapy, or known dihydropyrimidine dehydrogenase (DPD) deficiency

• Known hypersensitivity to platinum compounds or any of the components of the study medications

• Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to study treatment start, or anticipation of the need for major surgical procedure during the course of the study; fine needle aspiration within 7 days prior to study treatment start. When required, central venous line placement for chemotherapy administration must have been inserted at least 2 days prior to treatment start

• Current or recent (within 10 days prior to study treatment start) use of full-dose oral or parenteral anticoagulants or thrombolytic agent. Low dose warfarin was permitted provided INR≤ 1.5

• Chronic, daily treatment with high-dose aspirin (>325mg/day) or nonsteroidal anti-inflammatory medications (those known to inhibit platelet function at doses used to treat chronic inflammatory diseases).

• Received any investigational drug or agent/procedure, *i.e*. participation in another trial, within 4 weeks before beginning treatment with study drug.

These selection criteria and the application of the randomization process produced treatment groups well balanced for demographic, disease and treatment characteristics as shown in Table 8 below.

Table 8: Characteristics of patients recruited into the NO16966 study

	Treatment allocation					
	FOLFOX (N=317)	**P-FOLFOX (N=351)**	**B-FOLFOX (N=349)**	**XElOX (N=317)**	**P-XElOX (N=350)**	**B-XElOX (N=350)**
Demographics						
Gender						
Male	204 (64%)	186 (53%)	205 (59%)	194	205	213
Female	113 (36%)	165 (47%)	144 (41%)	(61%)	(59%)	(61%)
				123	145	137
				(39%)	(41%)	(39%)
Race						
Caucasian	236 (74%)	312 (89%)	300 (86%)	237	312	313
Black	4 (18%)	7 (2%)	11 (3%)	(75%)	(89%)	(89%)
Oriental	-	0	-	8 (3%)	5 (1%)	5 (1%)
Other	77 (24%)	32 (9%)	38 (11%)	-	-	-
				72 (23%)	33 (9%)	32 (9%)
Age						
Mean (years)	60.6	58.8	59.7	60.3	59.1	59.7
Range Years)	24-83	26-83	19-82	24-84	18-83	18-86
ECOG PS (baseline)						
0	163 (51%)	211 (60%)	198 (57%)	160	207	207
1	154 (49%)	138 (40%)	147 (43%)	(50%)	(59%)	(59%)
2	-	-	-	157 50%)	143	142
				-	(41%)	(41%)
					-	1 (<1%)
Alkaline Phosphatase (baseline)						
Abnormal	135 (43%)	147 (42%)	146 (42%)	132	149	156
Normal	182 (57%)	201 (58%)	199 (58%)	(42%)	(43%)	(45%)
				183	200	191
				(58%)	(57%)	(55%)
Disease characteristics						
Time from diagnosis with mCRC to randomization						
Mean (days)	104.6	95.9	88.0	76.5	83.0	90.7
Range (days)	1-2868	1-1571	0-1401	0-899	0-2437	2-2813
Number of metastatic sites						
>1	118	142	150	127	155	134
=1	(37.2%)	(40.5%)	(43.0%)	(40.1%)	(44.3%)	(38.3%)
	198	208	198	190	195	216
	(62.5%)	(59.3%)	(56.7%)	(59.9%)	(55.7%)	(61.7%)
Liver metastases?						
Yes						
No	238	269	266	241	261	272
	(76.3%)	(76.7%)	(76.0%)	(76.0%)	(74.6%)	(77.7%)
	75 (23.6%)	82 (23.4%)	84 (24.0%)	76	89	78
				(24.0%)	(25.4%)	(22.3%)
Treatment history						
Prior adjuvant therapy?						
Yes	83 (26%)	85 (24%)	88 (25%)	58 (28%)	91 (26%)	76 (22%)
No	234 (74%)	266 (76%)	261 (75%	229	259	274
				(77%)	(71%)	(78%)
Treatment for metastatic disease						
First						
Second	296 (93%)	333 (95%)	332 (95%)	301	334	333
	21 (7%)	18 (5%)	16 (5%)	(95%)	(95%)	(95%)
				16 (5%)	16 (5%)	17 (5%)

6.7.2.2 Study population for E3200

Patients 18 years of age or over with measurable, histologically confirmed, advanced or metastatic adenocarcinoma of the colon or rectum were eligible for study entry. Prior treatment with a fluoropyrimidine and irinotecan, either separately or in combination for advanced disease and recovery from any treatment-related toxicities were required. Patients had to have adequate hepatic, renal and haematologic function. An ECOG performance status of 0-2 was specified. These entry criteria and the randomisation procedure adopted produced a study population that was well balanced across the two study arms of interest as shown in Table 9 below.

Table 9: Characteristics of patients recruited to the FOLFOX and B-FOLFOX arms of the ECOG3200 study

	Treatment allocation	
	FOLFOX (n=292)	**B-FOLFOX (n=293)**
Demographics		
Age		
Mean (SD)	60.3 (10.7)	61.3 (11.0)
Range	25-84	21-85
Gender		
Male	177 (60.6%)	177 (60.4%)
Female	115 (39.4%)	116 (39.6%)
Race		
Caucasian	257 (88.0%)	256 (87.4%)
Black	20 (6.8%)	25 (8.5%)
Oriental	3 (1.0%)	1 (0.3%)
Other	12 (4.1%)	12 (4.1%)
ECOG PS (baseline)		
0	148 (50.9%)	141 (48.1%)
>/=1	143 (49.1%)	126 (51.6%)
Disease characteristics		
CEA (baseline)		
Abnormal	30 (10.3%)	26 (9.1%)
Normal	261 (89.7%)	250 (90.9%)
Number of disease sites		
1	88 (30.1%)	87 (29.7%)
>1	204 (69.9%)	206 (70.3%)
Liver metastases?	221 (75.7%)	
Yes	71 (24.3%)	214 (73.0%)
No		79 (27.0%)
Treatment history		
Prior adjuvant chemotherapy	232 (79.5%)	230 (78.5%)
Prior chemotherapy for advanced disease	223 (76.4%)	230 (78.4%)

6.7.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

NO16966

At the time of clinical cut-off for the final analysis on January 31st 2006 of 2035 patients randomised 904 had died, 38 had been lost to follow-up and the remainder were alive and in various stages of study treatment and post-treatment follow up. However, at this point data were immature for overall survival and to support regulatory submissions a further analysis was carried out with a data cut-off of 31st January 2007. At this point 1179 of 2034 patients (58%) had died. This analysis (the 4-months Safety Update Report 1026598; 4MSU), mature for overall survival forms the basis of this submission unless otherwise stated. A CONSORT flow chart giving details of the disposition of patients randomised into Study NO16966 is shown in Figure 7 below.

E3200

At the time of final analysis (1st August 2005) 525 deaths had occurred amongst the 585 patients randomised to the two principal study arms (FOLFOX+/-B) with no patients still receiving protocol directed therapy. The detailed disposition of patients in E3200 is shown in figure 8 below.

Figure 7: CONSORT diagram showing disposition of patients enrolled in study NO16966

No. screened= Not available

↓

No. randomised = 2035 (1 randomised twice included in arm for which he signed consent and was treated)

↓

	FOLFOX	**P-FOLFOX**	**B-FOLFOX**	**XELOX**	**P-XELOX**	**B-XELOX**
Randomised to arm	317	351	349	317	350	350
Received allocated treatment	313 (99%)	336 (96%;6 rcvd B-FOLFOX)	335 (96%)	316 (100%)	339 (97%; 4 rcvd B-XELOX	349(100%)
↓	↓	↓	↓	↓	↓	↓
Withdrew consent	3	2	9	2	9	4
Lost to follow-up	10 (3.2%)	3 (0.9%)	12 (3.4%)	12 (3.8%)	6 (1.7%)	7 (2.0%)
Alive in follow-up	42 (13.2%)	121 (34.5%)	113 (32.4%)	53 (16.7%)	97 (27.7%)	120 (34.3%)
Alive in post-study phase	-	1 (0.5%)	6 (1.7%)	-	7 (2.0%)	8 (2.3%)
Dead	262 (82.6%)	224 (63.8%)	209 (59.9%)	250 (78.9%)	231 (66.0%)	211 (60.3%)
↓	↓	↓	↓	↓	↓	↓
Included in ITT efficacy analysis	317 (100%)	351 (100%)	349 (100%)	317 (100%)	350 (100%)	350 (100%)

Figure 8: CONSORT diagram showing the disposition of patients enrolled in study E3200

Patients assessed for inclusion= not available

↓

Patients Randomised= 829

↓

	FOLFOX	**B-FOLFOX**	**B alone**
Randomised to arm	292	293	244
Received allocated treatment	285 (97.6%)	287 (98.0%)	806 (97.2%)
Not treated	7 (2.4%)	6 (2.0%)	10 (4.1%)
Died	0 (0%)	1 (0.3%)	2 (0.8%)
Ineligible	1 (0.3%)	0 (0%)	0 (0%)
Refused treatment	5 (1.7%)	2 (0.7%)	5 (2.0%)
Other	1 (0.3%)	3 (1.0%)	3 (1.2%)

↓

No patients remaining on study treatment at time of analysis. Reasons for withdrawal:-

CR or PR followed by resection	3 (1.0%)	3 (1.0%)	1 (0.4%)
Progression/relapse During treatment	147 (50.3%)	141 (48.1)	159 (65.2%)
Toxicity/side-effects/complications	69 (23.6%)	66 (22.5%)	28 (11.5%)
Death on study	7 (2.4%)	12 (4.1%)	6 (2.5%)
Withdrew/refused treatment	21 (7.2%)	28 (8.5%)	5 (2.0%)
Alternate therapy	4 (1.4%)	5 (1.7%)	2 (0.8%)
Intercurrent illness	3 (1.0%)	4 (1.4%)	2 (0.8%)
Other	30 (10.3%)	31 (10.6%)	29 (11.9%)
Not stated	1 (0.3%)	0 (0%)	1 (0.4%)

↓

Included in ITT efficacy analysis	292 (100%)	293 (100%)	244 (100%)

6.7.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from prespecified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

6.7.4.1 Study end-points in NO16966

Primary

PFS (superiority of bevacizumab plus chemotherapy over chemotherapy and non-inferiority of XELOX+/-B *versus* FOLFOX+/-B). PFS was defined as the time from the date of randomisation to the first day of documented disease progression or death due to any cause. The schedule of assessment of disease progression is shown in Table 7, above.

Secondary:

These included:

Efficacy

- PFS for superiority of XELOX over FOLFOX
- Overall Survival
- Overall Rate of Best Response (Using RECIST criteria)
- Time to Response
- Duration of Response
- Duration of Complete Response
- Time to Treatment Failure

Safety

- Adverse events
- Serious adverse events
- Dose modifications
- Premature withdrawal from treatment etc

6.7.4.2 Study end-points in E3200

Primary.

The primary efficacy end-point was a comparison of overall survival (time from randomisation to death from any cause) in the principal arms defined in the Study Statistical Analysis Plan as FOLFOX and B-FOLFOX.

Secondary.

These included:

- Response Rate (using RECIST Criteria)
- PFS, defined as the time from randomisation to disease progression or death from any cause within 30 days following discontinuation of protocol therapy
- Duration of response, defined as time from the first tumour assessment that met the criteria for objective response, as assessed by the ECOG Coordinating Center, to the time of disease progression or death from any cause within 30 days of following discontinuation of protocol therapy.
- Safety

6.7.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were preplanned or post-hoc.

6.7.5.1 NO16966 study

Analysis populations

Efficacy

In accordance with convention, for non-inferiority end-points, the eligible patient population (EPP) was used for the primary analysis and for superiority end-points the intent to treat (ITT) population was used. Exploratory analyses were also conducted using whichever of the ITT and EPP was not used for the primary analysis. EPP and ITT were defined as follows:-

ITT

This population included all randomized patients who provided written informed consent.

Patients in the ITT population were analyzed according to the arm to which they were randomized.

EPP

The eligible patient population excluded patients from the ITT who had violated major protocol inclusion or exclusion criteria or:

- • patients randomized under the initial 2-arm part of the study and who did not receive at least one dose of capecitabine, 5-FU, or oxaliplatin
- • patients randomized under the 2x2 factorial part of the study and who did not receive at least one dose of capecitabine, 5-FU, oxaliplatin, or bevacizumab/placebo.

Safety

The primary population for safety purposes (the Safety Population) comprised of all patients receiving any study treatment.

Analysis history

Database snapshots were taken on October 28th, 2005 and November 23rd, 2005 for the purpose of event tracking. There were 1233 and 1323 events of PFS, respectively, at these time-points. This represented an event rate of approximately 90 events per month. Based on this, it was expected that 1,500 events in the overall ITT population would occur by the end of January 2006, ensuring the 1,200 PFS events required in the EPP required to achieve 90% power, at a time when all patients would have been followed for a minimum of 12 months. Therefore, the clinical cut-off for the final analysis was set to January 31, 2006.

A further, updated analysis was carried out for regulatory purposes ("4 Months Safety Update Report 1026598; 4MSUR) with a clinical cut-off date of 31st January 2007 at which point 1179 deaths had occurred amongst the 2034 patients in the study (58% dead). This analysis, which includes mature data on the secondary end-point of Overall Survival, forms the basis of the efficacy and safety analyses included in this submission, as well as the pharmacoeconomic analysis unless otherwise stated.

Statistical methods

An interaction test was performed on the primary endpoint of PFS to detect any kind of interaction between the different regimens (FOLFOX, XELOX, placebo or bevacizumab) and to justify pooling of data for comparison of the primary study end-points as described above (superiority of PFS comparing chemotherapy plus placebo

with chemotherapy plus bevacizumab and non-inferiority of PFS comparing FOLFOX arms with XELOX arms) . The interaction test was repeated for the two secondary parameters of overall survival (based on Cox proportional hazards regression) and overall rate of best response (based on logistic regression). The study statistical plan stated that for testing non-inferiority for the primary endpoint of PFS, the hazard ratio (HR) and associated 97.5% confidence interval (CI) were calculated based on a proportional hazards model. Non-inferiority was concluded if the upper limit of the two-sided 97.5% CI for the HR did not exceed 1.23. Non-inferiority hypotheses were also tested for the secondary endpoints. Superiority of bevacizumab in combination with chemotherapy (B-XELOX, B-FOLFOX) to chemotherapy alone (P-XELOX, P-FOLFOX) was based on the stratified log-rank test and used a two-sided significance level of 2.5%.

Although, not part of the original statistical plan for the study the lack of a placebo effect identified during interaction testing allowed the pooling of patients receiving chemotherapy alone (XELOX or FOLFOX) with those receiving FOLFOX or XELOX plus placebo in the second part 2 x 2 part of the study. An analysis on data pooled in this way was done during development of the economic model used in this submission, because the larger patient numbers permit the determination of the treatment impact of adding bevacizumab to chemotherapy to be determined with greater precision.

6.7.5.2 E3200 study

Analysis populations

Two main study populations were defined for analysis purposes. The Efficacy Population consisted of all patients randomised into the study (i.e. analysis was conducted on an ITT basis) and the Safety Population consisted of all patients receiving any study medication.

Analysis history

As per the study protocol, recruitment was suspended and data reviewed for safety issues after 50 patients had been recruited to each arm was reviewed for safety issues, the Data Safety Monitoring Committee (DSMC) saw no reason to modify the study at this stage. A further informal review of efficacy data by the DSMC ahead of the first formal interim analysis resulted in the DSMC recommending closure of the bevacizumab alone arm. This recommendation was carried out on 11th March 2003. Two formal interim analyses were carried out as specified in the trial protocol. The first was carried out on the 27th April 2004 and did not result in any recommendation to modify the conduct of the study. The second showed that the study data now satisfied the criterion for early stopping as set out in the study statistical plan and the study was closed. The data base was transferred from ECOG to Genentech (Roche's development partner for Avastin) on 1st August 2005 and this represents the clinical cut-off for the results presented in this submission.

Statistical methods

The primary efficacy endpoint for this study was duration of survival, defined as the time from randomisation to death from any cause. All reported deaths were included in the analysis. Duration of survival for patients who were not known to have died at the time of analysis was censored at the date the patient was last known to be alive.

Duration of survival was formally compared between B-FOLFOX and FOLFOX arms using the two-sided stratified log-rank test. Kaplan-Meier methodology was used to estimate median duration of survival for each treatment arm. The HR for death on the B-FOLFOX arm relative to the FOLFOX arm was estimated using a stratified Cox regression model. The stratification factors were baseline ECOG performance status (0, >/=1) and prior radiation therapy (yes, no). Stratification factors were determined from data collected on the Case Report Form. The Type 1 error rate for the comparison of the principal arms for the primary endpoint of duration of survival was alpha=0.0167 (two-sided). To control the Type 1 error rate for the primary end-point of duration of survival, accounting for two formal interim analyses of efficacy, the Lan and DeMets implementation of the O'Brien-Fleming alpha-spending function was used.

6.7.6 Critical appraisal of relevant RCTs

The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study meeting the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- How was allocation concealed?
- What randomisation technique was used?
- Was a justification of the sample size provided?
- Was follow-up adequate?
- Were the individuals undertaking the outcomes assessment aware of allocation?
- Was the design parallel-group or crossover? Indicate for each crossover trial whether a carry-over effect is likely.
- Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?
- How do the included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.
- For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?
- Were the study groups comparable?
- Were the statistical analyses used appropriate?
- Was an intention-to-treat analysis undertaken?

- Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?

Criterion	Primary study NO16966	Supportive study ECOG E3200
How was allocation concealed?	In the assessment of bevacizumab efficacy a matched placebo was used to which patients and investigators were blind. For the comparison of oral capecitabine and IV 5-FU placebo control was impractical and unethical (widespread use of IV placebo). Therefore, patients and clinicians were unblinded to treatment allocation. However, primary end-point was objective (tumour shrinkage on a scan) and the investigator assessment of response was checked using radiologists blind to treatment allocation	This was an open label study. However, the primary study end-point of Overall Survival is not liable to investigator bias
What randomisation technique was used?	Acceptable. Centralised, using IVRS system – see Section 6.3.1.3 for details	Acceptable, based on limited informationCentralised by the ECOG Co-ordinating Center
• Was follow-up adequate?	Yes. Analyses for primary end-point (PFS) and overall survival was event-driven as specified in the statistical plan.	Yes. Study was stopped at a protocol specified interim analysis which demonstrated that as specified in the trial SAP the O'Brien-Fleming boundary for the primary end-point had been crossed with alpha controlled at 0.00167. A Final Analysis for survival was subsequently conducted when 91% of FOLFOX and 89% of B-FOLFOX patients had died with a median follow-up of 25.0 and 28 months, respectively.
• Were the individuals undertaking the outcomes assessment aware of allocation?	The primary analysis was based on investigator assessment of PFS. Investigators were blinded to treatment allocation of bevacizumab or placebo,	No, but this was irrelevant to the primary end-point in this study (overall survival)

	but not to the allocation of XELOX *versus* FOLFOX. A supportive analysis conducted by independent reviewers blind to all treatment allocation was conducted.	
Was the RCT conducted in the UK (or were one or more centres of the multinational RCT located in the UK)? If not, where was the RCT conducted, and is clinical practice likely to differ from UK practice?	This was a multinational study conducted by 216 investigators from 32 countries including the UK. The principal investigator on the study was Prof James Cassidy from the Beatson Oncology Centre in Glasgow. Clearly Prof Cassidy felt that the protocol was relevant and appropriate for UK clinicians and patients.	No. This study was conducted in the USA. The main difference between the study population in the USA and the UK is probably in the first-line treatment that they received. In the UK (see Table 3) the predominant first-line chemotherapy is oxaliplatin plus a fluoropyrimidine. In the USA at the time of the study it was IFL (irinotecan, 5-FU, FA) making it logical to examine the role of FOLFOX+/-B in the second-line setting. Thus data from this second-line study are being used to support UK use in the first-line setting. This is acceptable given the general view, supported by NICE guidance, that the sequence of oxaliplatin and irinotecan-based chemotherapies for the first two lines of treatment for metastatic CRC is unimportant.
How do those included in the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting	The patient population represents one that is relevant from a UK perspective – patients with metastatic CRC, with a slight excess of males over females receiving their first treatment for metastatic colorectal cancer with a combination of a fluoropyrimidine and oxaliplatin (the predominant first-line treatment in the UK). The obvious difference from the general population of UK patients *diagnosed* with metastatic CRC is that	

	they are slightly younger – 83% of patients diagnosed with colorectal cancer in the UK are over 60 years of age, whereas the mean age of recruits to the present study is 59.7 years. However, this is probably more typical of the fitter, younger patients who would receive combination chemotherapy with oxaliplatin-based combinations in this country	
For pharmaceuticals, what dosage regimens were used in the RCT? Are they within those detailed in the Summary of Product Characteristics?	Yes. The dose of 7.5 mg/kg bevacizumab every 3 weeks accords with the SPC dose range. Doses of cytotoxic agents used accord with the relevant SPC's and UK clinical practice.	Yes. The dose of 10 mg/kg bevacizumab every 2 weeks accords with the SPC dose range. Doses of cytotoxic agents used accord with the relevant SPC's and UK clinical practice.
Were the study groups comparable?	Yes. See Table 8	Yes See Table 9
Were the statistical analyses used appropriate?	Yes. The studies were analysed in accordance with the predetermined statistical plan prepared by statisticians.	Yes. The studies were analysed in accordance with the predetermined statistical plan prepared by statisticians.
Was an intention-to-treat (ITT) analysis undertaken?	Yes – primary superiority analyses (bevacizumab *versus* placebo) were done on an ITT basis with primary non-inferiority analyses (XELOX *versus* FOLFOX) done on a Per Protocol Population basis as is appropriate	Yes – primary superiority analyses (bevacizumab *versus* placebo) were done on an ITT basis

• Were there any confounding factors that may attenuate the interpretation of the results of the RCT(s)?	None known	None known

6.8 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- The number of patients included in the analysis.
- The median follow-up time of analysis
- State whether intention-to-treat was used for the analysis and how data were imputed if necessary.
- Discuss and justify definitions of any clinically important differences.
- Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

6.8.1 Overall results from Study NO16966

6.8.1.1 Test of treatment interaction

Prior to proceeding with the analysis of this study, the statistical test for interaction between the treatments (FOLFOX, XELOX, placebo or bevacizumab) was carried out. This was based on Cox proportional hazards regression which is a two-sided test with a significance level of 5%. If the event of a statistically significant result, the null hypothesis of no interaction would have be rejected and it would have been concluded that there was a statistically relevant interaction.

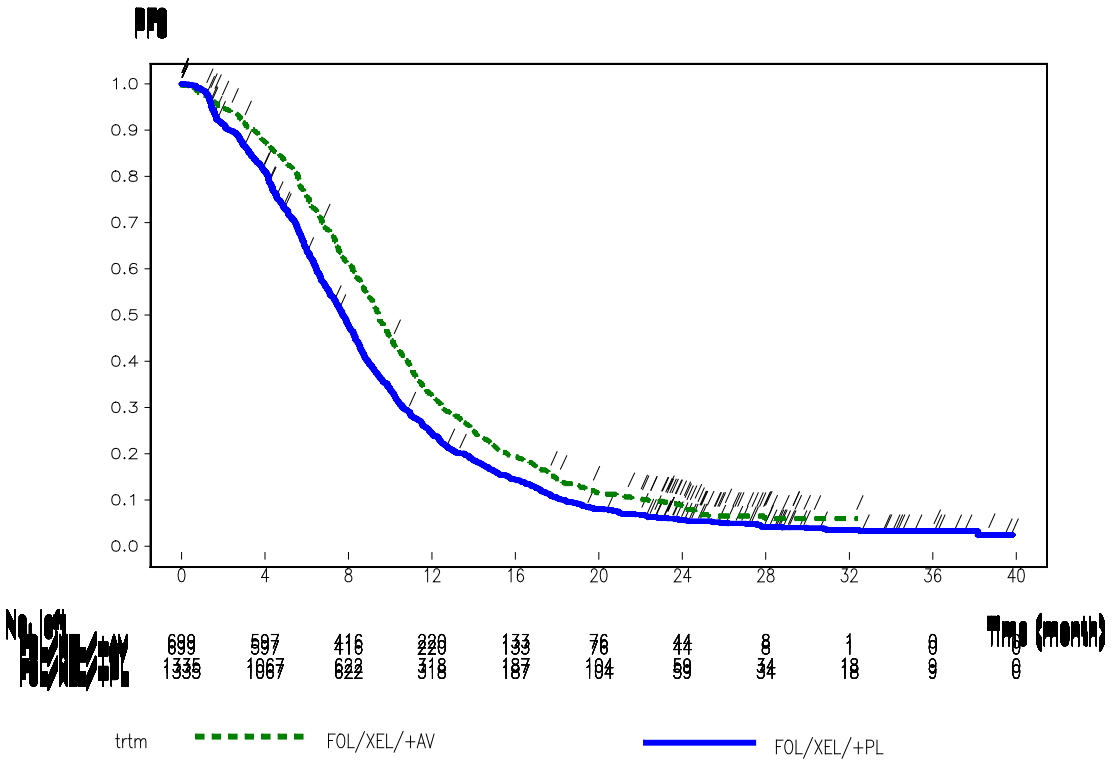
For PFS the test resulted in a p-value of 0.7025 indicating that a statistically significant interaction could be excluded. Similarly, for the secondary end-point of overall survival a p-value of 0.9380 resulted. The absence of interaction permitted the planned pooling of XELOX and FOLFOX regimens when examining the impact of bevacizumab and regimens with and without bevacizumab when testing the effect of switching from FOLFOX to XELOX and the inclusion of patients from the original chemotherapy alone arms with the corresponding chemotherapy+placebo bevacizumab arms in order to increase statistical power.

6.8.1.2 Impact on progression-free survival of adding bevacizumab to chemotherapy

In the pooled ITT comparison of chemotherapy plus bevacizumab (B-XELOX/B-FOLFOX) *versus* chemotherapy alone (XELOX/P-XELOX/FOLFOX/P-FOLFOX) carried out for economic modelling the addition of bevacizumab significantly improved PFS. The risk of disease progression was reduced by 21% (HR=0.79, 955% CI 0.72, 0.87; p=0.0001) and median PFS increased from 7.7 to 9.4 days. The improvement in PFS resulting from the addition of bevacizumab to oxaliplatin-based chemotherapy is shown graphically in Figure 9. When the analysis was restricted to patients in second 2x2 part of the study, as per the original statistical plan, the reduction in the risk of progression was 17% (HR 0.83; 95% CI 0.72-0.95; P=0.0023) with median PFS increased from 8.0 to 9.4 months.

Thus the first of the two co-primary end-points of the study was met.

Figure 9: Improvement in progression-free survival when bevacizumab was added to oxaliplatin-based chemotherapy in study NO16966



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16JUL2009 17:45

Abbreviations: F, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-XELOX; X+P, P-XELOX;

6.8.1.3 Impact on progression-free survival of replacing FOLFOX with XELOX in Study NO16966

In the EPP comparison of XELOX (+/- bevacizumab or placebo) *versus* FOLFOX (+/- bevacizumab or placebo) PFS in the XELOX group met the protocol specified criterion for non-inferiority relative to FOLFOX (that the upper limit of the 97.5% CI should be below 1.23), the second co-primary end-point in this study. The HR was 1.02 with 97.5% CI 0.92, 1.14. Median PFS was 259 days in the FOLFOX group and 242 days in XELOX recipients. Similar results were obtained when data from the ITT population was used. In this case the HR was 1.01 (97.5% CI 0.91, 1.12) and median PFS was 259 days and 244 days for the FOLFOX and XELOX groups, respectively. Thus the second of the study's two co-primary end-points was met.

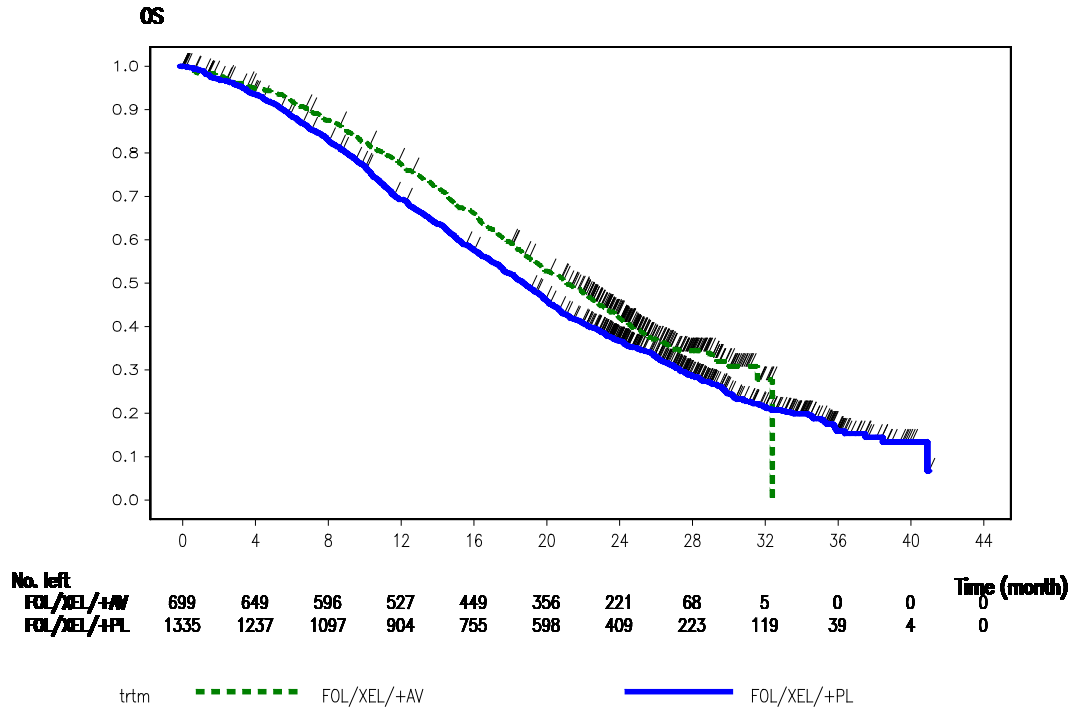
6.8.1.4 Impact on overall survival of adding bevacizumab to chemotherapy

In the pooled ITT comparison of chemotherapy plus bevacizumab (B-XELOX/B-FOLFOX) *versus* chemotherapy alone (XELOX/P-XELOX/FOLFOX/P-FOLFOX) carried out for the construction of the economic model used in this submission, the addition of bevacizumab significantly improved OS. The risk of death was reduced by 17% (HR=0.83, 95% CI 0.74, 0.93; p=0.0019) and median OS increased from 18.9 to 21.2 months. The improvement in OS resulting from the addition of bevacizumab to oxaliplatin-based chemotherapy is shown graphically in Figure 8. When the analysis was restricted to patients in second 2x2 part of the study, as per the original statistical plan, a similar trend towards improved survival was seen. The risk of death was reduced by 11% (HR 0.89; 95% CI 0.76-0.1.03; P=0.0769) with median PFS increased from 19.9 to 21.3 months.

Analysis of Efficacy by Treatment Subgroup (intent-to-treat population)

Figure 10: Improvement in overall survival when bevacizumab was added to oxaliplatin-based chemotherapy in study NO16966

Protocol(s): I16966M
Analysis: INTENT TO TREAT POPULATION
Filter Applied: WHERE ECTYPEN LE 4



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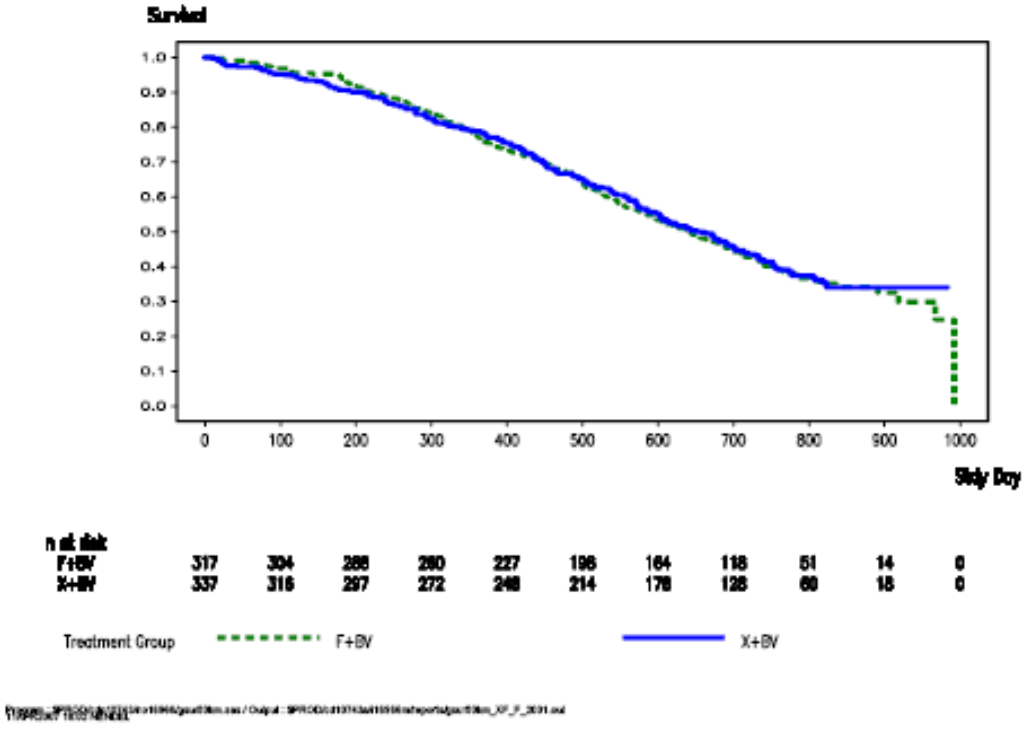
Abbreviations: F, FOLFOX; F+BV, B-FOLFOX; F+P, P-FOLFOX; X, XELOX; X+BV, B-XELOX; X+P, P-XELOX;

6.8.1.5 Impact on overall survival of replacing FOLFOX with XELOX in Study NO16966

In the EPP comparison of XELOX (+/- bevacizumab or placebo) *versus* FOLFOX (+/- bevacizumab or placebo) OS in the XELOX group met the protocol specified criterion for non-inferiority relative to FOLFOX (that the upper limit of the 97.5% CI should be below 1.23). The HR was 1.00 with 97.5% CI 0.88, 1.13. Median PFS was 594 days in the FOLFOX group and 600 days in XELOX recipients. Similar results were obtained when data from the ITT population was used. In this case the HR was 0.99 (97.5% CI 0.88, 1.12) and median OS was 596 days and 602 days for the FOLFOX and XELOX groups, respectively. The similarity in OS when XELOX and FOLFOX-based regimens were used is shown graphically in Figure 7.

Figure 11: Overall survival in the FOLFOX and XELOX arms of study NO16966



The results just described (coupled with the lack of interaction between treatments described in Section 6.4.1.1) demonstrates that, in terms of efficacy:

- XELOX and FOLFOX can be assumed to be a therapeutically equivalent baseline regimens
- Adding bevacizumab improves outcomes to a similar extent when added to either chemotherapy regimen and so:
- A patient receiving either B-XELOX or B-FOLFOX can be expected to experience similar outcomes as a result of receiving similar benefit from bevacizumab

superimposed on similarly active baseline chemotherapy

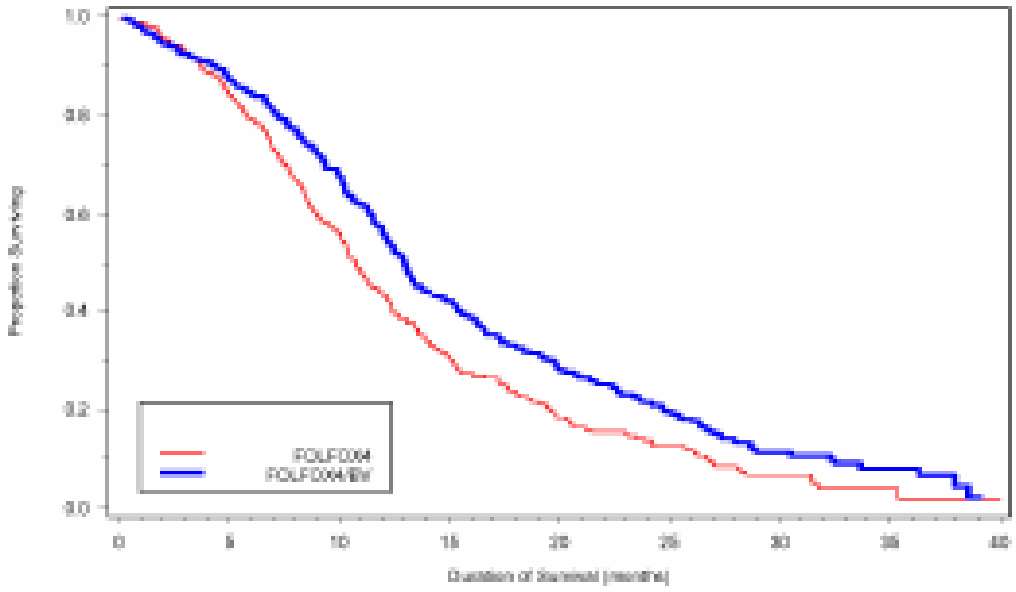
6.8.2 Impact of adding bevacizumab to oxaliplatin-based chemotherapy in patients with liver metastases in NO16966

- Because metastatic colorectal cancer is, in most cases incurable, there has been particular interest in recent years in the group of patients who have metastatic disease restricted to the liver and which may be surgically resected at presentation or after cytotoreductive chemotherapy. Prof James Cassidy, one of the principle investigators on NO16966, and colleagues have presented an analysis of the impact of bevacizumab added to oxaliplatin and fluoropyrimidine chemotherapy on patients with liver metastases in the NO16966 study. They reported an R0 (i.e. removal of metastasis/ses with a margin of healthy tissue) resection rate of 4.9% for patients receiving chemotherapy alone and 6.3% for patients receiving chemotherapy plus bevacizumab. Although this difference did not reach statistical significance it may be clinically important since achieving an R0 resection has great value to patients. In their presentation Cassidy *et al* reported than for the majority of patients without R0 resection, 2 year survival was 37.9% (95% CI 34.1-41.7) after treatment with chemotherapy + placebo and 39.6% (95% CI 35.7-43.5) after chemotherapy plus bevacizumab. However, for patients with an R0 resection, 2 year survival increased to 82.3% (95% CI 69.4-95.1) on chemotherapy and 90.9% (95% CI 82.4-99.4) on bevacizumab plus chemotherapy. Thus R0 resection is of immense value to patients and the addition of bevacizumab appears to increase both R0 resection rates and outcomes after resection.6.4.5 Supportive evidence from Study E3200.

6.8.2.1 Overall survival in Study E3200

- The addition of bevacizumab to FOLFOX chemotherapy reduced the risk of death by 24.9% (HR 0.751; 95% CI 0.332, 0.893; log-rank p-value 0.0012) with median OS increased from 10.8 to 13.0 months. Thus the primary study end-point was improved to a clinically and statistically significant extent, as illustrated in Figure 10.

Figure 12: Overall survival for patients receiving FOLFOX and B-FOLFOX in study E3200



Abbreviations: FOLFOX4/BV, B-FOLFOX

Secondary endpoints in study E3200 were also improved by a clinically relevant and statistically significant extent as shown in Table 6.

Table 10: Impact of adding bevacizumab to FOLFOX chemotherapy on secondary efficacy end-points in study E3200.

	FOLFOX (n=292)	B-FOLFOX (n=293)	p-Value
Progression-free survival			
Patients with event	179	177	
Disease progression	169	160	
Death	10	17	
Median progression-free survival (months) 95% CI	4.5 (4.07, 5.26)	7.5 (6.77, 8.18)	
Hazard ratio (95% CI)	0.518 (0.416, 0.646)		<0.0001 log-rank
Tumour response			
Complete response rate	2 (0.7%	5 (1.7%)	
Partial response rate	23 (7.9%)	60 (20.5%)	
Overall response rate [95% CI] 95% CI	25 (8.6%) (5.7%, 12.5%)	65 (22.2%) (17.6%, 27.5%)	<0.0001 Cochran, Mantel-Haenszel

6.9 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 6.6.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis where appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

No new meta-analysis has been carried out for this submission. Since Roche are proposing a very specific change in standard therapy from XELOX or FOLFOX to B-XELOX or B-FOLFOX, the NO16966 study is the only one to provide data specifically addressing this issue. However, a mixed treatment comparison and meta-analyses

have been published which lend broad support to the proposition that, in the treatment of metastatic colorectal cancer, adding bevacizumab to chemotherapy in general and oxaliplatin/fluoropyrimidine combinations, in particular, improves outcomes.

A recent meta-analysis has been published by Cao *et al.*(2009) This specifically addresses the issue of the impact of adding bevacizumab to chemotherapy for metastatic colorectal cancer and its impact on OS, TTP/PFS, RR and safety. This meta-analysis appears to have been well conducted. The authors began with a broad search strategy, interrogating an appropriate (and described) set of scientific literature databases for articles including the words bevacizumab/Avastin and colorectal cancer. They then selected from these randomised clinical trials of chemotherapy *versus* chemotherapy with the addition of bevacizumab. This process identified 9 RCTs of which only 5 met the (defined) entry criteria. The quality of these studies was assessed by the authors who described them as "reasonably well designed and conducted" with the mean Jadad score for the included studies being 2. Formal assessment of heterogeneity between the included studies was carried out and significant heterogeneity was detected which, on the basis of sensitivity analysis, was attributed largely to one study.

The authors found that the addition of bevacizumab improved, by a statistically significant extent, all three of the efficacy parameters reviewed. They also considered that the improvements were clinically meaningful and that the benefit of bevacizumab more than justified the approximately 10% increase in Grade 3/4 adverse events.. Results are summarised in Table 7.

Table 11: Results of the meta-analysis by Cao et al. comparing chemotherapy with and without the addition of bevacizumab for metastatic colorectal cancer.

Parameter	p-value for heterogeneity	Hazard Ratio (95% CI)	p-value
Overall Survival	0.08	0.77 (0.67-0.89)	0.00
Progression (PFS/TTP)	0.00	0.66 (0.56-0.77)	0.02
Response rate	0.00	1.55 (1.06- 2.10)	0.02
Incidence Grade III/IV toxicity	>0.10	1.79 (1.52-2.11)	0.00

6.10 Indirect/mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. An 'indirect comparison' refers to the synthesis of data from trials in which the technologies of interest have not been compared in head-to-head trials, but have been compared indirectly using data from a network of trials that compare the technologies with other interventions.

When head-to-head RCTs exist, evidence from mixed treatment comparison analyses may be presented if it is considered to add information that is not available from the head-to-head comparison. A 'mixed treatment comparison' refers to an analysis that includes trials

that compare the interventions of interest head-to-head and trials that compare them indirectly. This mixed treatment comparison must be fully described and presented as additional to the reference-case analysis (a 'mixed treatment comparison' includes trials that compare the interventions head-to-head and indirectly).

When multiple technologies are being appraised that have not been compared within a single RCT, data from a series of pairwise head-to-head RCTs should be presented. Consideration should also be given to presenting a combined analysis using a mixed treatment comparison framework if it is considered to add information that is not available from the head-to-head comparison.

The principles of good practice for standard meta-analyses should also be followed in mixed and indirect treatment comparisons.

- When evidence is combined using indirect or mixed treatment comparison frameworks, trial randomisation must be preserved. Where this is not possible the data should be treated as observational.
- Provide a clear description of the methods of synthesis
- Provide a rationale for the identification and selection of the RCTs, including the rationale for the selection of treatment comparisons that have been included.
- Perform a statistical assessment of heterogeneity. The degree of, and the reasons for, heterogeneity should be explored as fully as possible
- The methods and results of the individual trials should be documented. If there is doubt about the relevance of a particular trial, sensitivity analysis should also be presented in which these trials are excluded.
- The heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies should be reported.
- Evidence from a mixed treatment comparison may be presented in a variety of ways such as in tables or diagrams.

Golfinopoulos *et al* 2007 published a comprehensive meta-analysis of treatments for metastatic colorectal cancer. The authors took as their reference regimen 5-FU and FA and categorised treatments according to use or no use of 5-FU, irinotecan, oxaliplatin, bevacizumab and oxaliplatin. Their end-points of interest were overall survival and progression-free survival.. The approach used was robust and consisted of identifying studies by a systematic search of the scientific literature and using clearly defined criteria including or excluding them from the final analysis. The authors' approached initially identified 22,512 potentially relevant articles, from which were identified 242 RCTs for systematic review which, in turn yielded 40 suitable for multiple treatment meta-analysis or mixed treatment comparison (MTC). Statistical methodology used was clearly reported, including analysis of heterogeneity and the authors state that their reporting is in accordance with QUOROM guidelines. The main limitation of this article from the perspective of the current appraisal is its age, which means that whilst it included the ECOG E3200 study it did not include results from the NO16966 trial.

As shown in Table 8, Golfinoupoulos found that compared with 5-FU/FA alone the greatest survival benefit was conferred by the addition of bevacizumab and irinotecan to the treatment regimen This was followed by the combination of 5-FU/FA/oxaliplatin/bevacizumab, for which the 95% Confidence Interval for the HR largely overlapped with that for the irinotecan/5-FU/FA/bevacizumab combination

Table 12: Comparison of OS in mixed treatment comparison of chemotherapy regimens for advanced colorectal cancer by Golfinopoulos et al (2007)

	All comparisons* (n=47)	First-line comparisons (n=31)	Non-first-line comparisons (n=10)	Non-bolus comparisons† (n=25)
Fluorouracil and leucovorin‡ + irinotecan + bevacizumab	0·60 (0·44–0·84)	0·60 (0·44–0·81)	..	..
Fluorouracil and leucovorin‡ + irinotecan + oxaliplatin	0·72 (0·54–0·97)	0·72 (0·54–0·93)	..	0·70 (0·53–0·89)
Fluorouracil and leucovorin‡ + oxaliplatin + bevacizumab	0·72 (0·57–0·90)	0·74 (0·57–0·97)	0·68 (0·20–1·89)	0·76 (0·62–0·92)
Fluorouracil and leucovorin‡ + bevacizumab	0·78 (0·60–1·03)	0·78 (0·61–1·00)	..	..
Fluorouracil and leucovorin‡ + oxaliplatin	0·87 (0·78–0·98)	0·84 (0·74–0·94)	0·90 (0·44–1·57)	0·91 (0·81–1·02)
Irinotecan + oxaliplatin	0·89 (0·67–1·19)	0·87 (0·67–1·13)	..	1·10 (0·83–1·45)
Fluorouracil and leucovorin‡ + irinotecan	0·92 (0·84–1·01)	0·91 (0·83–1·00)	0·86 (0·37–2·03)	0·89 (0·80–0·97)
Bevacizumab	0·92 (0·66–1·25)	..	0·96 (0·29–2·68)	1·00 (0·75–1·28)
Irinotecan	1·00 (0·86–1·17)	1·17 (0·95–1·46)	0·84 (0·42–1·60)	0·92 (0·77–1·06)
Oxaliplatin	1·00 (0·67–1·54)	0·88 (0·43–1·83)	1·08 (0·47–2·46)	0·96 (0·64–1·45)

*Number of distinctive treatment comparisons (multi-arm studies contribute more than one comparison). †Oral fluoropyrimidine analogues are included in the non-bolus regimens. ‡Fluorouracil and leucovorin: fluorouracil plus leucovorin, or oral fluoropyrimidine analogue. Data are HR (with 95% credibility intervals) for death for each type of regimen as compared with fluorouracil-based chemotherapy with leucovorin (without irinotecan, oxaliplatin, bevacizumab, or cetuximab). Data are shown for the analysis of all eligible trials, of trials comparing only first-line treatments, of trials comparing only second-line and third-line treatments, and of trials not containing any bolus fluorouracil plus leucovorin monotherapy or combination arm.

For the comparison of PFS the combinations of 5-FU+FA+bevacizumab+irinotecan or oxaliplatin were again the most effective regimens in the MTC, and the advantage of using combination chemotherapy plus bevacizumab (as reflected in the hazard ratio) was even greater using this end-point, as shown in Table 9.

Table 13: Comparison of PFS in mixed treatment comparison of chemotherapy regimens for advanced colorectal cancer by Golfinopoulos et al (2007)

	All comparisons* (n=42)	First-line comparisons (n=32)	Non-first-line comparisons (n=10)	Non-bolus comparisons† (n=26)
Fluorouracil and leucovorin‡+irinotecan+bevacizumab	0·41 (0·28–0·60)	0·41 (0·29–0·59)	..	..
Fluorouracil and leucovorin‡+oxaliplatin+bevacizumab	0·46 (0·34–0·61)	0·56 (0·39–0·80)	0·32 (0·15–0·65)	0·47 (0·36–0·60)
Fluorouracil and leucovorin‡+irinotecan+oxaliplatin	0·53 (0·38–0·73)	0·54 (0·40–0·73)	..	0·51 (0·38–0·69)
Fluorouracil and leucovorin‡+bevacizumab	0·56 (0·41–0·76)	0·56 (0·42–0·75)	..	..
Fluorouracil and leucovorin‡+irinotecan+cetuximab	0·62 (0·42–0·92)	0·63 (0·44–0·91)	..	0·60 (0·43–0·84)
Fluorouracil and leucovorin‡+oxaliplatin	0·64 (0·56–0·73)	0·68 (0·59–0·77)	0·52 (0·33–0·78)	0·65 (0·56–0·74)
Fluorouracil and leucovorin‡+irinotecan	0·73 (0·65–0·82)	0·74 (0·66–0·83)	0·74 (0·38–1·43)	0·70 (0·61–0·80)
Irinotecan+oxaliplatin	0·76 (0·56–1·01)	0·84 (0·61–1·16)	0·57 (0·26–1·25)	0·82 (0·59–1·08)
Irinotecan	1·07 (0·88–1·30)	1·23 (0·97–1·56)	0·82 (0·52–1·37)	0·88 (0·67–1·16)
Bevacizumab	1·08 (0·72–1·58)	..	0·90 (0·42–1·87)	1·13 (0·76–1·55)
Oxaliplatin	1·42 (1·08–1·86)	1·37 (0·89–2·09)	1·34 (0·79–2·18)	1·35 (1·00–1·79)

*Number of distinctive treatment comparisons (multi-arm studies contribute more than one comparison). †Oral fluoropyrimidine analogues were included in the non-bolus regimens. ‡Fluorouracil and leucovorin: fluorouracil plus leucovorin, or oral fluoropyrimidine analogue. Data are HR (with 95% credibility intervals) for progression for each type of regimen as compared with fluorouracil-based chemotherapy with leucovorin (without irinotecan, oxaliplatin, bevacizumab, or cetuximab). Data are shown for the analysis of all eligible trials, of trials comparing only first-line treatments, of trials comparing only second-line and third-line treatments, and of trials not containing any bolus fluorouracil plus leucovorin monotherapy or combination arm.

Also important from the perspective of this appraisal is the finding that combinations of 5-FU+FA+oxaliplatin and 5-FU+FA+irinotecan are similar in efficacy, with the

oxaliplatin based regimens, if anything, slightly more effective. If this is correct then anyone who is changed from 5-FU+FA+irinotecan to oxaliplatin-based chemotherapy plus bevacizumab can expect to get as much or more incremental benefit as a patient moving from oxaliplatin-based chemotherapy to oxaliplatin-based chemotherapy plus bevacizumab.

6.11 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials.

Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

Background

This section utilises safety data from the randomised study NO16966. NO16966 provides comparative data on the safety impact of adding bevacizumab, at the proposed dose, to the two oxaliplatin-based chemotherapy regimens of interest (XELOX and FOLFOX). The ECOG 3200 study which supports the efficacy part of this submission is of limited value in considerations of safety since it provides no information on the B-XELOX regimen and the study employed a dose of bevacizumab twice that proposed for use in UK clinical practice. This is important given that the two hallmark toxicities of bebacizumab (hypertension and proteinuria) are dose-related.

The NO16966 study demonstrates that the efficacy of the XELOX and FOLFOX chemotherapy regimens are the same and both are enhanced to the same extent by the addition of bevacizumab. If NICE recommends that bevacizumab should be available to NHS patients who would currently receive oxaliplatin-based chemotherapy alone, it would be reasonable for a clinician to choose B-XELOX or B-FOLFOX based on efficacy considerations alone. Under this circumstance it is possible that, in future, a patient who would, today, receive FOLFOX might, in future, receive B-XELOX. Therefore, it is important to consider the safety implications not only of adding bevacizumab to oxaliplatin-based chemotherapy but also of a move from FOLFOX to XELOX. This section will use the safety data from NO16966 to examine both of these changes.

Impact of adding bevacizumab to oxaliplatin-based chemotherapy in NO16966

Table 10 shows adverse events amongst patients receiving oxaliplatin-based chemotherapy with and without bevacizumab and highlights (in bold type) those that occurs with an absolute frequency 5% or more higher or lower than in patients receiving bevacizumab.

There are small, but greater than 5% reductions, in the rates of “blood and lymphatic disorders” and “neutropenia and granulocytopenia” which are not particularly to be

expected from the pharmacology of bevacizumab and may be a chance observation. Bevacizumab was also associated with 5% or greater increases in the rate of all-grade stomatitis, hand-foot syndrome, bleeding problems, infections and infestations, venous thromboembolic events, and hypertension. Of these, the first four are adverse events generally associated with cytotoxic chemotherapy and it is likely that their increased incidence is a consequence of longer chemotherapy treatment duration amongst bevacizumab recipients (treatment was continued until disease progression and time to disease progression was increased by the inclusion of bevacizumab in the treatment regimen).

The >5% increases the other three all-grade adverse events (bleeding problems, thromboembolic events and hypertension) were predictable from the known pharmacology of bevacizumab and clinical experience with the drug in other studies. They were amongst a set of 6 protocol-specified “adverse events of special interest for bevacizumab”:

Hypertension

Proteinuria

Bleeding

GI perforation, intrabdominal sepsis and fistula

Thromboembolic events

Wound healing complications

The frequency of all “adverse events of special interest” was 55% (16% grade 3/4) amongst bevacizumab recipients and 41% (9% grade 3/4) amongst patients receiving chemotherapy alone, indicating that although these events were of interest the majority of them could not be attributed be bevacizumab.

A review of Table 10 shows that although all of the events of special interest were numerically more common amongst bevacizumab recipients, the excess was generally small and, importantly, most cases were of mild-moderate severity so that there were very few additional cases of Grade 3-4 (severe/life-threatening) events in these categories. The clearest effects of adding bevacizumab were an increase in low-grade hypertension and proteinuria with small increases in the overall frequency of Serious Adverse Events from 22.1% to 26.2% and life-threatening adverse events from 18.6% to 23.5%.

Patient impact of adding bevacizumab to oxaliplatin-based chemotherapy

Overall, the patient implications of adding bevacizumab to oxaliplatin-based chemotherapy are limited. The most likely impact on them is an increase in low-grade hypertension and asymptomatic proteinuria, the latter usually associated with the former. Management consists of monitoring blood pressure during routine clinic visits with periodic urine testing for protein using a dip-stick test. Hypertension, when it is considered to require treatment, usually responds to standard antihypertensive

drugs. Resolving hypertension will normally reduce excessive levels of protein in the urine.

Other indirect measures of any negative patient impact of adding bevacizumab to chemotherapy are the rates of treatment discontinuation because of adverse events (25.5% without and 30.1% with bevacizumab) and treatment related deaths -2.1% without, 2.2% with. Both of these measures suggest that the potential for patients suffering significant treatment toxicity from added bevacizumab to their oxaliplatin-based chemotherapy is low.

Impact of substituting FOLFOX with XELOX in NO16966

The impact of substituting FOLFOX with XELOX, is shown in Table 11, which demonstrates this change reduces, by more than 5%, in absolute terms, the incidence of all-grade blood and lymphatic disorders, stomatitis, neutropenia/ granulocytopenia, bleeding problems and infections/infestations but results in a >5% increase in the incidence of hand-foot syndrome. This picture is very familiar from other situations where capecitabine consistently results in less stomatitis and damage to the bone marrow (and, hence, infections and bleeding problems) but more hand-foot syndrome (drying, redness and soreness of the palmar and plantar surfaces of the hands and feet) relative to regimens of 5-FU+FA. It also increases the incidence of diarrhoea somewhat. Although the increase in all-grade diarrhoea is below 5%, grade 3 and 4 diarrhoea exceeds this threshold. This almost certainly drives the increase in Grade 3 and 4 gastrointestinal disturbances which, along with Grade 3 hand-foot syndrome were the only Grade 3 and 4 with an excess incidence 5% or more in XELOX patients relative to FOLFOX patients. On the other hand, blood and lymphatic disorders and granulocytopenia/neutropenia were more than doubled in patients receiving FOLFOX compared with XELOX– these increases in haematological toxicity can be assumed to underpin the increased rates of Grade 3 and infection/infestation and febrile neutropenia in FOLFOX patients compared with those receiving XELOX.

Patient impact of replacing FOLFOX with XELOX

In terms of the patient's experience when receiving XELOX-based rather than FOLFOX-based treatment, the most likely negative aspects are an increased incidence of diarrhoea and hand-foot syndrome. Both of these adverse events are uncomfortable and/or inconvenient, but seldom (almost never in the case of hand-foot syndrome) life-threatening. Moreover, oncologists treating colorectal cancer are now very experienced in prescribing capecitabine, which has been widely used in the UK for the last decade so that they are very adept at supplying adjunctive therapies and modifying doses to prevent early, modest toxicity turning into something more serious. On the benefit side, a move from FOLFOX to XELOX will reduce the levels of neutropenia and related infections that patients experience. In particular the rate of febrile neutropenia will fall, reducing the chances of a patient requiring an emergency admission to hospital in order to receive treatment with antibiotics for an infection superimposed on a period of profound immunosuppression.

In addition, patients receiving B-XELOX do not automatically require the permanent central venous access device mandated for the prolonged 5-FU infusions needed for FOLFOX. Apart from sparing patients the trauma of line insertion and the restrictions that such a line puts on their everyday life (the need to keep the line clean, dry and

secure can severely limit everyday and recreational activities) getting rid central venous access devices removes an entry point for systemic and entry site infections and a nucleus for thrombotic problems.

If the overall safety and tolerability of treatment is measured in deaths judged to be treatment-related and treatment discontinuations as a consequence of adverse events then the FOLFOX and XELOX arms of NO16966 were very similar. 26.7% and 27.8% of FOLFOX and XELOX recipients, respectively, stopped treatment in response to an adverse event and 2.1% and 2.4%, respectively experienced a death described as treatment related.

Finally, when considering the combination of bevacizumab plus oxaliplatin-based chemotherapy, there is no clear relationship between the frequency of “adverse events of special interest for bevacizumab, as detailed above, and chemotherapy regimen, indicating that bevacizumab is similarly well tolerated when added to either XELOX or FOLFOX. One possible exception is the somewhat higher rate of all-grade bleeding events seen when bevacizumab is added to FOLFOX relative to XELOX. This may reflect an exacerbation of bevacizumab’s tendency to cause low-grade bleeding problems by the greater reduction in platelet numbers caused by FOLFOX compared with the less myelotoxic XELOX.

Table 14: Safety impact of adding bevacizumab to chemotherapy in study NO16966

	All grade		Grade 3/4	
	Treatment allocation			
Adverse event	**Chemotherapy alone N=1303 n (%)**	**Chemotherapy + Bevacizumab N=695 n (%)**	**Chemotherapy alone N=1303 N (%)**	**Chemotherapy+ Bevacizumab N=695 n (%)**
Any	1293 (99.2)	691 (99.4)	974 (74.8)	**55 (79.9)**
Any Related	1282 (98.3)	685 (98.6)	288 (22.1)SAEs	182 (26.2) SAEs
Gastrointestinal Disorders	1209 (92.8)	645 (92.8)	383 (29.4)	219 (31.5)
Blood and Lymphatic Disorders	760 (58.3)	**354 (50.9)**	422 (32.4)	203 (29.2)
Diarrhoea	823 (63.2)	443 (63.7)	207 (15.9)	121 (17.4)
Nausea/vomiting	916 (70.3)	487 (70.1)	99 (7.6)	63 (9.1)
Stomatitis	382 (29.3)	**244 (35.1)**	21 (1.6)	19 (2.7)
Neutropenia/granulocytopenia	559 (42.9)	**259 (37.2)**	328 (25.2)	163 (23.5)
Febrile neutropenia	37 (2.8)	19(2.7)	37 (2.8)	19 (2.7)
Hand/foot syndrome	271 (20.8)	**188 (27.1)**	48 (3.7)	48 (6.9)
Neurotoxicity	1049 (80.5)	577 (83.0)	221 (17.0)	125 (18.0)
Gastrointestinal perforation	4 (0.3)	4 (0.5)	4 (0.3)	4 (0.5)
Bleeding problems	307 (23.6)	**212 (30.5)**	20 (1.5)	13 (1.8)
Venous thromboembolic events	94 (7.2)	**92 (13.2)**	66 (5.1)	54 (7.8)
Arterial thromboembolic events	17 (1.3)	17 (2.4)	12 (1.0)	12 (1.7)
Hypertension	57 (4.4)	**132 (19.0)**	10 (0.8)	28 (4.0)
Proteinuria	24(1.8)	35 (5.0)	12 (1.0)	4 (0.6)
Wound healing complications	14 (1.1)	12 (1.7)	4 (0.3)	3 (0.4)
Fistula or intra-abdominal abscess	10 (0.7)	14 (2.0)	9 (0.7)	6 (0.9)
Cardiac disorders	67 (5.1)	54 (7.8)	15 (1.1)	37 (5.3)
Infections/infestations	501 (38.4)	**300 (43.2)**	111 (8.5)	51 (7.3)

Note: Frequencies in bold are 5% higher or lower in absolute terms than for chemotherapy without bevacizumab.

Table 15: Safety impact of chemotherapy allocation in study NO16966

Adverse event	All grade		Grade 3/4	
	Treatment allocation			
	FOLFOX/P-FOLFOX/B-FOLFOX N=990 n (%)	XELOX/P-XELOX/B-XELOX N=1008 n (%)	FOLFOX/P-FOLFOX/B-FOLFOX N=990 n (%)	XELOX/P-XELOX/B-XELOX N=1008 n (%)
Any	984 (99.4)	1000 (99.2)	388 (39.2)	368 (36.5)
Any Related	976 (98.6)	991 (98.3)	232 (23.4)	238 (23.6)
			SAE	
Gastrointestinal Disorders	923 (93.2)	931 (92.4)	254 (25.7)	**342 (33.9)**
Blood and Lymphatic Disorders	**677 (68.4)**	437 (43.4)	**477 (48.2)**	229 (22.7)
Diarrhoea	613 (62.0)	653 (64.8)	118 (12.0)	**210 (20.8)**
Nausea/vomiting	687 (69.4)	716 (71.0)	72 (7.3)	90 (8.9)
Stomatitis	**384 (38.8)**	242 (24.0)	25 (2.5)	15 (1.5)
Neutropenia/granulocytopenia	**568 (57.4)**	250 (24.8)	**420 (42.0)**	71 (7.0)
Febrile neutropenia	46 (4.6)	10 (1.0)	46 (4.6)	10 (1.0)
Hand/foot syndrome	117 (11.8)	**342 (33.9)**	14 (1.4) G3	**82 (8.1) G3**
Neurotoxicity	796 (80.4)	830 (82.3)	168 (17.0)	178 (17.7)
Gastrointestinal perforation	2 (0.2)	6 (0.6)	2 (0.2)	6 (0.6)
Bleeding problems	**301 (30.4)**	218 (21.6)	14 (1.4)	19 (1.9)
Venous thromboembolic events	99 (10.0)	87 (8.6)	73 (7.3)	47 (4.7)
Arterial thromboembolic events	19 (1.9)	15 (1.5)	13 (1.3)	11 (1.1)
Hypertension	107 (10.8)	82 (8.1)	17 (1.7)	21 (2.1)
Proteinuria	40 (4.0)	19 (1.9)	3 (0.3)	13 (1.3)
Wound healing complications	18 (1.8)	8 (0.8)	4 (0.4)	3 (0.3)
Fistula or intra-abdominal abscess	16 (1.6)	8 (0.8)	9 (0.9)	6 (0.6)
Cardiac disorders	63 (6.4)	58 (5.6)	32 (3.2)	20 (2.0)
Infections/infestations	**455 (46)**	346 (34.3)	96 (9.7)	66 (6.5)

Note: Frequencies in bold are 5% higher in absolute terms than for other chemotherapy group

6.12 Non-RCT evidence

6.13 Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available.

6.14 Inferences about relative treatment effects drawn from non-RCT evidence will necessarily be more circumspect than those from RCTs with properly controlled evidence. The bias that may be present in non-randomised data means the results should be interpreted cautiously. When possible, the use of more than one independent source of such evidence needs to be examined to gain some assurance of the validity of any conclusions drawn.

6.14.1 Details of how the relevant non-RCTs have been identified and selected

Three regimens of Eloxatin Evaluation (TREE) study

The TREE study was identified during literature searching for RCT evidence. It was evident during scrutiny of citations that although it was not a randomised study of chemotherapy with or without bevacizumab, the design of the TREE study was such as to provide helpful supportive information on the use of oxaliplatin-based chemotherapy with and without bevacizumab in a well-defined and uniform patient population.

Bevacizumab Expanded Access Trial (BEAT) study

BEAT was a study well known to the bevacizumab team within Roche and was included because it included information that it was felt complemented that provided by the Phase III trials identified during literature searching. The current focus on surgical excision of isolated hepatic metastases as one of the few interventions that yields long-term survivors amongst patients with metastatic colorectal cancer means that growing importance is being attached to the selection of pre-operative drug treatment to render otherwise inoperable metastases amenable to surgery. Therefore, it was felt relevant to include in this submission data on hepatic resection from the BEAT study. This study was designed to collect safety and efficacy data on bevacizumab plus first-line chemotherapy in a less selected cohort of first-line patients than are generally recruited to clinical trials. In particular, by recruiting a large cohort of patients it was anticipated that the study would provide useful further information on uncommon or rare adverse events. However, it is also one of

relatively few studies to prospectively collect data on hepatic resection, this being the reason for its inclusion here.

Bevacizumab Regimens: Investigation of Treatment Effects and Safety (BRiTE)

The BriTE study was also familiar to the bevacizumab experts at Roche. It was a large observational study of bevacizumab-containing first-line systemic drug treatment for metastatic colorectal cancer. Its unique value is in providing a measure of the efficacy of oxaliplatin-based chemotherapy plus bevacizumab in a population of patients unselected for the criteria usually applied to patients recruited to clinical studies and resembling those encountered in clinical practice. As such it provides reassurance that the clinical trial results already described can be achieved in routine patient management.

6.14.2 Summary of methodology of relevant non-RCTs

TREE study

The TREE (Three Regimens of Eloxatin Evaluation) study was originally designed as a randomised comparison of the tolerability of three different combination regimens of oxaliplatin and a fluoropyrimidine used for the first-line chemotherapy of metastatic colorectal cancer (the TREE-1 cohort). It opened for recruitment in November 2002. As recruitment neared completion evidence was emerging of the value of adding bevacizumab to combination chemotherapy for metastatic colorectal cancer and a protocol amendment was made allowing for the recruitment of a further cohort (the TREE-2 cohort) randomised between the same three chemotherapy regimens with the addition to each of bevacizumab administered at a dose of 5 mg/kg IV every two weeks. Recruitment to the TREE-1 cohort was closed in November 2003 when 50 patients had been recruited to each arm and between November 2003 and April 2004 223 patients were recruited into the TREE-2 cohort. Thus although TREE does not include randomisation between chemotherapy alone or with bevacizumab it does provide evidence of the efficacy of oxaliplatin-based chemotherapy with and without bevacizumab at the proposed dose in two very similar cohorts of patients treated, largely, in the same centres and recruited over a relatively short period of time. As such the TREE study provides useful supportive information in this appraisal.

Patients were recruited from multiple centres exclusively in the USA. Key entry criteria for both TREE-1 and TREE-2 were as follows:-

- Age 18 years or over giving informed consent
- Histologically documented metastatic or recurrent colorectal cancer
- No prior chemotherapy for metastatic/recurrent disease (adjuvant chemotherapy with 5-FU/FA+/-irinotecan more than 6 months before study entry acceptable)
- ECOG performance status 0 or 1
- Adequate haematological, hepatic and renal function
- No recent history of myocardial infarction
- No current significant cardiac disease, interstitial lung disease or significant lung fibrosis
- In addition entrants to TREE-2 were required to have:
- Haemoglobin >/= 8g/dL
- Normal blood coagulation parameters
- Urinary protein excretion less than +1 on dipstick testing

Patients were randomised between three different chemotherapy regimens as shown in Table 15 below.

Table 16: Treatment regimens used in the TREE study

Regimen name	Drugs received TREE-1 cohort	TREE-2 Cohort
mFOLFOX 6+/-B	Day 1 Oxaliplatin 85 mg/m^2 IV + FA 350mg IV over 2 h + 5-FU 400 mg/m^2 IV bolus Day 1-2 5-FU 2400 mg/m^2 infused IV over 46 hours Repeat every two weeks	As TREE-1 plus bevacizumab 5mg/kg IV on Day 1
bFOL+/-B	Days 1 and 15 Oxaliplatin 85 mg/m^2 IV over 10-20 min Days 1, 8 and 15 FA 20 mg/m^2 IV over 10-20 min followed by 5-FU 500 mg/m^2 IV bolus Repeat every 4 weeks	As TREE-1 plus bevacizumab 5mg/kg IV on Days 1+15
XELOX+/-B	Day 1 Oxaliplatin 130 mg/m^2 IV Days 1-15 Capecitabine 1,000 mg/m^2 twice daily by mouth Repeat every 3 weeks	As TREE-1 except capecitabine dose reduced to 850mg/m^2 twice a day and bevacizumab 7.5 mg/kg IV added on Day 1

For all three regimens treatment was continued until disease progression or unacceptable toxicity.

The primary endpoint in the TREE study was safety. In the final version of the protocol (as amended to allow the recruitment of the TREE-2 cohort) the primary endpoint was the incidence of Grade 3/4 adverse events for each treatment arm

compared with the relevant no bevacizumab treatment group from the TREE-1 cohort. Secondary endpoints included:

- Adverse events during the first 12 weeks of treatment on TREE-1
- All AE's within 30 days of treatment
- Overall response rate based on RECIST criteria
- Time to disease progression (defined as time from randomisation to disease progression or death from any cause)
- Time to treatment failure (time from randomisation to disease progression, death from any cause or discontinuation of all study treatment)
- Overall survival (time from randomisation to death from any cause)

The study was powered to detect a 15% increase in Grade 3/4 adverse events using a one-group chi-squared test with a nominal one-sided 0.05 significance level and 80% power within the 50% to 70% adverse event rate of historical controls. All study analyses were conducted on the "as-treated" population which included all randomly assigned patients receiving at least one treatment. Toxicities were recorded on day 1 of each cycle and additionally at the end of treatment.

Additionally, tumour assessments were carried at 12 week intervals in TREE-1 and at 6 week intervals in TREE-2. Responses were determined using RECIST criteria and confirmed by computed tomography or magnetic resonance imaging after 4-6 weeks. After treatment discontinuation TREE-2 patients were followed for survival at 3 monthly intervals for at least 2 years and 6 monthly, thereafter. Similar post-treatment follow up was collected on TREE-1 patients who consented to it retrospectively

The demographic and baseline characteristics of patients entered into the TREE study are shown in Table 16.

Table 17: Baseline and demographic characteristics of patients entered into the TREE study

Characteristic	TREE-1			TREE-2		
	mFOLFOX6 (%)	bFOL (%)	XELOX (%)	B-mFOLFOX6 (%)	B-bFOL (%)	B-XELOX (%)
No. of patients	49	50	48	71	70	72
Age, years						
Median	62	62	62.5	64	57	62
Range	35-79	31-84	32-84	31-83	30-85	32-82
Gender						
Female	43	38	35	39	51	42
Male	57	62	65	61	49	58
ECOG PS						
0	61	58	52	61	54	65
1	39	42	48	39	46	35
Prior adjuvant therapy	45	16	27	24	31	31
Primary site						
Colon	55	74	75	65	66	69
Colon/Rectum	27	14	19	17	11	24
Rectum	18	12	6	17	21	7
Other	0	0	0	1	1	0
Metastases						
Liver	76	76	65	73	74	83
Lung	47	50	50	42	41	44
Other	55	68	65	42	37	33

BEAT study

BEAT was an open-label, non-comparative trial open to patients 18 years of age with a good Performance Status (ECOG 0-1 or over) who had histologically confirmed metastatic colorectal cancer, scheduled to start first-line fluoropyrimidine based chemotherapy, adequate organ function and a life expectancy >3 months. Patients were excluded if they had received prior chemotherapy (other than in the adjuvant setting), planned radiotherapy (completed radiotherapy was acceptable), a history of other malignancies or surgery within 28 days prior to study entry, or planned at the time of study entry. Patients were also excluded if they had uncontrolled hypertension, clinically significant cardiovascular disease, bleeding diatehsis or coagulopathy, serious non-healing wounds or if they were receiving any of the following: full-dose anticoagulants or thrombolytics or drugs predisposing to GI ulceration including aspirin >325 mg/day. The study recruited 1965 patients from 376 centres in 41 countries worldwide (including the UK but excluding the USA) between July 2004 and February 2006.

Patients were treated with any chemotherapy regimen of the clinicians choosing that incorporated a fluoropyrimidine either alone or in combination with irinotecan or oxaliplatin plus bevacizumab at a dose of 5 mg/kg every 2 weeks (5-FU regimens) or 7.5 mg/kg every 3 weeks (capecitabine-based regimens) with treatment scheduled to continue until disease progression. The only formal study-mandated assessments after baseline recording of medical history were 3-monthly physical examination, haematology and serum chemistry, a urine dip-stick test for proteinuria within 48 hours of bevacizumab and PS evaluation. Data were collected prospectively on surgical procedures carried out during active study participation and their outcome. Other assessments were at the discretion of the investigators and should have been consistent with their routine clinical practice. Patients were ineligible for study entry if, in the opinion of the investigator, they had disease (including metastases) that were fully resectable at the time of entry *i.e.* if curative surgery was an option.

The primary study objective was the collection of safety data including uncommon or rare adverse events determined amongst all patients receiving at least one dose of study drug. Secondary end-points were OS (time from first bevacizumab administration to death), time to progression (TTP; time from start of first-line therapy to investigator-assessed progression) and PFS (time from the start of first-line therapy to investigator-assessed progression or death)

At the time of data analysis for publication (February 2008) data were available on 1914 patients who had received at least one dose of study drug. These patients had been followed for a median of 21.1 months (range 0-43.2 months) with 1845 (96%) having been followed for >60 days. The most common regimens were FOLFOX (29%), FOLFIRI (26%) and XELOX (18%); 16% of patients received fluoropyrimidine monotherapy.

BRiTE

BRiTE was an observational study conducted in patients scheduled to receive first-line chemotherapy plus bevacizumab for metastatic colorectal cancer (Grothey *et al.* 2007, 2008; Kozloff *et al.* 2006; Hedrick *et al.* 2006; Sugrue *et al.* 2006); . The only entry criterion apart from being scheduled to receive bevacizumab-containing first line treatment was that patients should have signed an informed consent form. There

were no other specific exclusion criteria or protocol-specified treatments or assessment techniques. Patients continued on study until death, withdrawal of consent or loss to follow-up.

Measures of outcome were similarly permissive and based on physician determination. They included time to progression from initition of first-line treatment to first PD; OS from the initiation of first-line treatment to death and survival beyond progression (from first progression to death) with data reporting every 3 months for up to 3 years and disease assessments made using the investigators method of choice . Safety outcomes focused on previously descrioibed bevacizumab-related events (hypertension, arterial thromboembolic events, bleeding events and GI perforation).

The study was sponsored by Genentech (the company responsible for developing and marketing bevacizumab in the USA; now part of Roche) who paid clinicians for data returns but not for bevacizumab or any other aspect of treatment. This arrangement removed any incentive to depart from routine pathways of care for patients in which was essentially an observational study.

Under these circumstances it seems reasonable to assume that BRiTE should give a good indication of the outcomes that can be achieved with bevacizumab-containing first-line treatment in a group ofpatients less selected than those in clinical trials and under conditions the same as in routine clinical practice. With regards to this, key strength of BRiTE are its size (it enrolled 1,953 patients from 248 study sites in 49 US states) and the very permissive entry criteria. Patients were able to participate if they met the following criteria: previously untreated metastatic colorectal cancer, treatment with bevacizumab first-line and signed informed consent. There were no other specific exclusion criteria or protocol-specified treatments or assessments. Patients continued on study until death, withdrawal of consent or loss to follow-up. Under these circumstances it seems reasonable to assume that BRite should give a good indication of the outcomes that can be achieved with bevacizumab-containing first-line treatment in a group ofpatients less selected than those in clinical trials and under conditions the same as in routine clinical practice.

The nature of BRiTE has already been described with clinical outcomes recorded from patients receiving bevacizumab-containing first-line treatment for metastatic colorectal cancer according to routine clinical practice in the centres concerned.

6.14.3 Critical appraisal of relevant non-RCTs

The TREE study was not originally designed to answer a question about bevacizumab, but to define the tolerability of 3 different oxaliplatin/fluoropyrimidine combinations. It was modified when almost complete to allow these same regimens with the addition of bevacizumab to be used and the primary end-point was redefined as a comparison of safety between the patients in TREE-2 receiving the same chemotherapy regimen (plus bevacizumab) as those in the TREE-1 cohort. As such the decision to treat with bevacizumab was not a random one. However there was no discretion (beyond omitting the patient from the trial) as the TREE-1 and TREE-2 cohorts were recruited consecutively, not simultaneously. Because of the nature of the study there was no concealment of treatment allocation, which was reasonable in

view of the primary safety end-point – administering placebo IV fluoropyrimidines to the XELOX arm may have resulted in adverse events not associated with the randomly allocated treatment.

In any cohort study the question arises as to whether patients in the cohorts are similar, since random allocation is not being used to enforce this. Table 16 shows no great differences between the TREE-1 and TREE-2 patients in age, gender or performance status. There are differences between the cohorts in the percentage of patients receiving adjuvant chemotherapy prior to study entry, most notably for patients in the mFOLFOX6 arms. However, these differences do not systematically favour the TREE-1 or TREE-2 cohorts (exposure to adjuvant chemotherapy might be expected to reduce the response to chemotherapy in the metastatic setting). Similarly, less patients in the TREE-2 cohort had metastatic disease in the lungs and in organs outside the lungs and liver. This might be expected to improve their prognosis a little. The additional inclusion criteria for TREE-2 relating to haemoglobin level, coagulation parameters and urinary protein excretion might be expected to result in slightly fitter patient group in the TREE-2 cohort. Disease assessment in TREE-1 was carried out every 12 weeks compared with every 6 in TREE-2. This would bias any assessment of TTF and PFS towards the TREE-1 cohort – if you don't assess disease as frequently you will not find early progression.

Another issue with sequential cohort studies of this type is the question of whether disease natural history or baseline care has changed between the recruitment of the cohorts, altering outcome independent of the study variable. In this case the two cohorts were recruited over a short time period, minimising this risk. In addition although some additional centres were involved in TREE-2, the treatment of colorectal cancer is fairly standard, particularly within the USA where all trial centres were located, and outcomes are not likely to have been significantly affected by this.

The study was conducted in the USA at a time before the use of cetuximab and bevacizumab became widespread there. Consequently, at the time North American treatments for metastatic colorectal cancer were broadly similar to those currently used within the UK, giving the study relevance to current UK practice.

All analyses in the published report of this study were based on the population of patients who had received at least one dose of study drug. Although this was entirely appropriate for the primary safety end-point of the study it is not ideal for efficacy analyses, with ITT analyses being preferred.

The dose of bevacizumab used in this study was the same as is being proposed for NHS use in this submission (equivalent to 2.5 mg/kg week).

Overall this study has significant weaknesses, but these are not such as to render it unfit for inclusion in this submission.

BEAT

This study was primarily designed to identify uncommon or rare adverse events and, as such required the recruitment of around 2,000 patients (Cassidy et al 2008; Cunningham et al 2008c; Van Cutsem *et al* 2009b). It was also considered desirable to recruit patients at a variety of centres worldwide. As such the data collection requirements were minimised. The minimal protocol requirements for standardised patient assessment are inconsistent with the usual approach to clinical trials and mean, for example, that some centres may identify progressing patients earlier than others or that transient, minor, adverse events may be under reported and, of course, there is no control arm, making it difficult to isolate the impact of treatment from underlying disease processes. However, despite these weaknesses the approach used in BEAT has some strengths in that the assessment approach mirrors that in clinical practice, where assessments are generally less frequent and undertaken to a less rigid timetable than in clinical trials. The data collected on hepatic resection were particularly interesting given that much of the published information on this subject refers to small case series treated in single centres.

BRiTE

The limitations of any uncontrolled observational study are clear. There can be no knowledge of exactly what outcomes would have been achieved in a similar cohort of patients not receiving bevacizumab and without standardisation of assessments it is impossible to rule out investigator bias in the assessment of tumour response and recording of toxicity. Despite this a permissive study of this size has some significant strengths. The minimal entry criteria would be expected to result in a study population less selected than those entering most interventional studies and more closely resembling those encountered in routine clinical practice. That this was the case, can be seen by comparing the baseline characteristics of patients entering BRiTE with those entering NO16966. Patients in BriTE were older (median 63.6 years *versus* 60 years) and less fit (42.9% PS 0; 42.2% PS2; 7.0% PS 2; 7.9% unknown *versus* 60%, 40% 0% and 0%).

The design of BriTE also gives a clear picture of clinicians' preferred first-line treatment regimens outside of clinical trials, for patients fit enough to receive bevacizumab.

6.14.4 Results of the relevant non-RCTs

TREE Study

The investigators in the TREE study concluded that each of the chemotherapy regimens used were of broadly similar tolerability and efficacy though there were qualitative differences between the regimens (more neutropenia with mFOLFOX, more hand-foot syndrome with XELOX) and that the addition of bevacizumab to chemotherapy adds little to the toxicity of chemotherapy. Details of their safety analysis will not be given here as it adds little to the more robust safety assessment that is possible using the large data set from the NO16966 study presented in section 6.7

As shown in Table 18, the addition of bevacizumab to each of the regimens used in TREE-1 resulted in numerical improvements in PR and CR rates, TTP and OS.

(statistical significance not stated in the publication). In addition when all TREE-1 patients are pooled the median OS was 18.2 months (95% CI, 14.5 to 21.6). This was 5.5 months less than the 23.7 (95% CI, 21.3 to 26.8) months achieved by the pooled TREE-2 patients.

Table 18: Efficacy outcomes in the TREE study

End-point	TREE-1 mFOLFOX6 (n=49)	bFOL (n=50)	CapeOx (n=48)	TREE-2 B-mFOLFOX6 (n=71)	B-bFOL (n=70)	B-CapeOx (n=72)
Response						
CR (%)	**0**	**0**	**2**	**6**	**6**	**3**
PR (%)	**41**	**20**	**25**	**46**	**33**	**43**
ORR (%)	**41**	**20**	**27**	**52**	**39**	**46**
Median TTP (months)	**8.7**	**6.9**	**5.9**	**9.9**	**8.3**	**10.3**
95% CI	**6.5 – 9.8**	**4.2 - 8.0**	**5.1-7.4**	**7.9 -11.7**	**6.6-9.9**	**8.6-12.5**
Median OS (months)	**19.2**	**17.9**	**17.2**	**26.1**	**20.4**	**24.6**
95% CI	**14.2-24.9**	**11.5-24.6**	**12.5-22.3**	**18.0-NE**	**18.4-25.3**	**21.4-31.6**
1 year survival (%)	**77.2**	**60.0**	**65.0**	**84.1**	**75.2**	**77.8**

BEAT

The investigators found that the safety profile of bevacizumab was consistent with that reported elsewhere, including clinical trials, with no new safety signals identified. Indeed they found that the rates of adverse events designated as being of "special interest" for bevacizumab (hypertension, proteinuria, bleeding, wound-healing complications, arterial thromboembolic events and GI perforation) were, generally, lower than those reported elsewhere. They speculate that this may be a consequence of increased awareness of the bevacizumab toxicity profile resulting in better patient selection and earlier and more appropriate intervention when it occurs. Similarly they found that efficacy of chemotherapy plus bevacizumab was similar to that reported elsewhere. Median PFS was 10.8 months (95% CI 10-11.3 months) and median OS was 22.7 (95% CI 21.7-23.8 months). These outcomes were similar for all combination chemotherapy regimens used, whilst combination chemotherapy regimens plus bevacizumab were, as expected, more effective than fluoropyrimidine monotherapy with the addition of bevacizumb. However, they did observe what appeared to be a differential effect of different regimens in rendering hepatic metastases operable. Overall curative hepatic metastatectomy was carried out in 145 patients (7.6% of the overall population) and was R0 (clear resection margins) in 114 (6%). The rate was higher amongst patients receiving oxaliplatin (10.4% resected; 8.0% R0) than amongst those receiving irinotecan (6.5%; 5.1% R0). For patients with

metastatic disease confined to the liver at baseline (n=704) the metastectomy rate reached 15.2% (12.1% R0) overall, 20.3% (15.4% R0) with oxaliplatin and 14.3% (11.7% R0) with irinotecan and the investigators suggest in their report that the magnitude of the difference indicates that oxaliplatin-based chemotherapy combined with bevacizumab may offer advantages over other regimens in patients who are candidates for surgery following effective reduction in the bulk of their hepatic metastases.

BRiTE

The study recruited 1968 patients from 248 sites in 49 states between Feb 2004 and June 2005 (Kozloff *et al* 2006- ammended to 1953 patients in Grothey *et al.* 2008). Cohort demographics were consistent with the NCI Surveillance, Epidemiology, and End Results (SEER) database for metastatic colorectal cancer, again indicating that the study poplation were representative of the generality of patients.

The most recent report of BRiTE was by Grothey *et al* in 2008 the authors reported median PFS of 10 months (range 0.03-33.6 months) and median OS of 25.1 months (95% CI, 23.4-27.5 months). The cut-off date for this analysis was January 2007, at which point the median follow-up was 19.6 months; 1,445 (74%) of patients had experienced progressive disease, 932 (47.7%) had died, 850 (44%) remained alive in follow-up; 74 (3.8%) had withdrawn from the study and 97 (5.0%) had been lost to follow-up.

The median PFS and OS in BriTE are very close to those reported for bevacizumab plus oxaliplatin-based chemotherapy in the NO16966 study (9.4 months and 21.3 months) indicating that the results in NO16966 study are achievable in a largely unselected patient population representative of routine clinical practice.

This most recent report also gives a breakdown of first-line chemotherapy regimens administered (FOLFOX 55.9%; FOLFIRI 14.3%; IFL, 9.7%; 5-FU bolus 6.8%; XELOX 4.8% and other 8.5%) indicating that in the USA as in the UK first-line combination chemotherapy is dominated by oxaliplatin-containing regimens, whilst few patients considered candidates for bevacizumab are treated with fluoropyrimidine monotherapy. Although Grothey *et al.* and their 2008 publication do not report on outcomes by regimen, an earlier conference presentation by the same authors does report on this question. Kozloff *et al* (2006) reported that after a median follow-up of 10 months that estimated median PFS was comparable in patients treated with chemotherapy regimens based on irinotecan (11.3 months) or oxaliplatin (11.4 and in patients receiving or 5-FU infusion (11.5 months), or capecitabine (11.6 months) as their flouropyrimidine. Patients receiving neither irinotecan nor oxaliplatin or bolus 5-FU as their fluoropyrimidine did rather less well. Although the estimated PFS values are rather longer than was seen with longer follow-up the relative values support the contention that bevacizumab produces similar clinical outcomes when added to irinotecan or oxaliplatin-based therapy, and that capecitabine produces the same outcome as infused 5-FU.

Grothey *et al.* (2008) also reported on adverse events of special interest to bevacizumab. The rates of new or worsened hypertension (19.4%), arterial thromboembolic events (1.7%), Grade 3 or 4 bleeding (1.8%) and GI perforation (1.4%) seen up to the time of first disease progression are remarkably similar to those seen in NO16966 (19.6%, 1.7%, 1.8% and 0.5%), indicating that the tolerability

of bevacizumab added to first-line chemotherapy for colorectal cancer was similar in patients treated as part of this observational study based on standard clinical practice as in those treated in the tightly controlled environment of a phase II registration trial.

6.15 Interpretation of clinical evidence

6.15.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice

Patients with metastatic colorectal cancer have limited life expectancy and although treatment aspirations vary between patients most would rate prolongation of survival as their most important treatment goal. Based upon the evidence presented above, the addition of bevacizumab to oxaliplatin-based chemotherapy consistently achieves prolongation of survival regardless of the specific oxaliplatin-based chemotherapy regimen used as the basis for treatment or the exact dose regimen of bevacizumab This has been demonstrated in individual studies such as NO16966, ECOG3200 and TREE and supported by meta-analyses and an MTC which demonstrate that adding bevacizumab to chemotherapy (including that based on oxaliplatin) consistently and convincingly improves survival by a clinically meaningful extent.

Similarly, although (as has already been explained in Sections 2 and 4) it is not envisaged that many UK patients who currently receive irinotecan-based therapy first-line are suitable for oxaliplatin-based treatment (with or without bevacizumab) analyses such as those by Golfinopoulos (2007) and NICE reassure that any who were, in future, moved from irinotecan-based chemotherapy to oxaliplatin-based chemotherapy plus bevacizumab would benefit to a similar extent to those where bevacizumab is added to their oxaliplatin-based treatment.

Until recently, metastatic colorectal cancer has been viewed as essentially incurable. However, there has been a growing realisation that for a small group of patients with metastatic deposits restricted to the liver, surgical removal of these metastases can result in long disease-free periods and, possibly, cure. Patients with resectable liver metastases at diagnosis are rare and clinicians regularly encounter individuals with tumour deposits that, though restricted to the liver, are too large for surgical removal. Under these circumstances, effective chemotherapy can render some patients operable and so it is highly relevant that, in meta-analysis, the addition of bevacizumab to oxaliplatin-based chemotherapy has been shown to increase tumour shrinkage as reflected in response rate. More directly, the addition of bevacizumab to oxaliplatin-based chemotherapy in NO16966 improved the R0 resection rate from 4.9% to 6.3%. Since it is R0 resections that are associated with long disease-free periods, this equates to almost one-third more patients becoming eligible for the only treatment that offers them a hope of cure. Over 90% of patients receiving oxaliplatin-based chemotherapy plus bevacizumab followed by R0 resection in the NO16966 study were still disease-free at 2 years, compared with 82.3% of those receiving chemotherapy alone and R0 resection. This highlights the value of R0 resection *per se*, and also indicates that even for those achieving it there may be an additional

benefit to receiving bevacizumab alongside oxaliplatin-based chemotherapy. That the combination of bevacizumab plus oxaliplatin-based chemotherapy is particularly good at increasing resection rates is also suggested by the BEAT study where hepatic resection rates reached 20.3% for those receiving oxaliplatin-based chemotherapy plus bevacizumab, compared with 14.3% for patients treated with irinotecan-based chemotherapy plus bevacizumab.

Although NICE has recently recognised the value of optimising chemotherapy regimens for patients with potentially resectable liver metastases and has approved cetuximab for use in this way, this is unlikely to be of much value for patients with K-ras mutations who show little benefit from cetuximab. Under these circumstances an alternative biologic agent that can be used with confidence that it will be equally effective regardless of K-ras status is much needed and highly relevant to patients. For some it will make the difference between being able to undergo, or not, potentially curative resection of their hepatic metastases.

For most patients, the length of time between starting treatment and disease progression is also a very important measure of treatment success. It represents a period during which, at minimum, they can expect that the signs and symptoms of disease that caused them to seek medical advice will not deteriorate, and the studies and meta-analyses presented in this submission provide convincing evidence that the addition of bevacizumab to oxaliplatin-based chemotherapy improves PFS compared with oxaliplatin-based chemotherapy and (by indirect evidence) irinotecan-based chemotherapy alone.

For patients with advanced cancer, quality of life (QoL) is also important – it is of no benefit to prolong life that is not valued by patients. It has been demonstrated repeatedly that effective chemotherapy for advanced colorectal cancer is associated with improved QoL (Colorectal Cancer Collaborative Group, 2000) and it can be assumed that this benefit will be seen with novel drug combinations, provided that the general benefits of treatment are not offset by increased toxicity or an unacceptably onerous administration schedule. Therefore, the comprehensive safety data collected in study NO16966 and elsewhere and meta-analysed by Cao *et al* (2009), demonstrating that B-XELOX and B-FOLFOX have similar tolerability to FOLFOX-4 and XELOX is highly relevant to patients.

6.15.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

There is little reason to believe that the clinical outcomes achieved in the NO16966 study, which provides the primary source of evidence for this submission, would not be achieved in UK clinical practice. The population of patients is one that is clearly

defined – patients requiring first-line chemotherapy for metastatic colorectal cancer – and one which would be well recognised by any colorectal oncologist working in this country. Although trial entry criteria required relatively good performance status (i.e. general fitness) it is generally only this group of patients who currently receive combination chemotherapy (i.e. comprising oxaliplatin or irinotecan plus a fluoropyrimidine, rather than a fluoropyrimidine alone), so that although the study patients may not be representative of all patients *diagnosed* with metastatic colorectal cancer, they are representative of those who currently receive oxaliplatin-based chemotherapy and who are thus candidates to receive additional bevacizumab as proposed here. The doses of chemotherapy and bevacizumab used in the NO16966 study correspond to those recommended in the bevacizumab SPC and (in the case of the concomitant cytotoxics) used in routine clinical practice.

Evidence that the results obtained in the NO16966 study should be reproducible in UK clinical practice is provided by the BriTE observation study of almost 2000 patients treated with first-line chemotherapy plus bevacizumab. This demonstrated that in group of patients unselected except on grounds of needing first-line chemotherapy plus bevacizumab and exhibiting characteristics of poorer prognosis than those usually entered into phase III clinical trials, efficacy outcomes and tolerability were very similar to those receiving B-FOLFOX or B-XELOX in NO16966.

Overall, it is possible to be confident that the introduction of bevacizumab into routine clinical practice within the NHS will result in health gains similar to those reported in the relevant trials.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

The strategy was designed to retrieve cost effectiveness studies which were relevant to the decision problem of bevacizumab (Avastin) for the treatment of first line metastatic colorectal cancer (mCRC). Search strategies did not include search terms or filters that would limit results to specific publication types or study design. In addition to broad medical databases (e.g., Medline and EMBASE), health economic databases and websites of health technology assessment (HTA) agencies were searched. All databases and websites searched are listed in Table 19. The search strategy is provided in Appendix 3.

Table 19: Literature review databases

General Databases
Medline
EMBASE
HTA/health economic databases and websites
NHS EED
Health Economic Evaluation Database (HEED)

7.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

Economic analyses were excluded if either they only evaluated resources used from a non-UK perspective and did not evaluate cost-effectiveness or did not include bevacizumab in combination oxaliplatin-based chemotherapy regimens in the evaluation. The search strategies are detailed in Appendix section 10 . The review identified two economic analyses of relevance.

Lewis et al

This study presented as a poster at ESMO 2008 was based on Roche's bevacizumab mCRC submission to the SMC that compared B-XELOX with FOLFOX-4. As with the economic analsys performed for this submission it was based on the results of the NO16966 study. The resulting ICER was £25,806. The main differences between the study and the analyis presented here is that a wider range of comparators were investigated within the scope of this appraisal and the results are presented in the context of the proposed APAS scheme.

Shiroiwa et al

This study published in 2007 investigated the cost-effectiveness analysis of bevacizumab combined with chemotherapy for the treatment of metastatic colorectal cancer in Japan. As this study was performed prior to the completion of the NO16966 RCT the authors commented *"It remains difficult to assess the first-line therapies comprising bevacizumab with oxaliplatin-based regimens, especially CAPOX* (XELOX). *No conclusions can be drawn until the results of the ongoing NO16966 trial—a large study with >2000 participants—are finally released."*

The authors were however able to investigate the cost effectiveness of second-line B-FOLFOX-4 vs FOLFOX-4 based on a Weibull regression of the publish survival curves from the E3200 study. Whilst it is considered that the cost results from this evaluation are unlikely to be applicable to this appraisal as they were not based on a UK NHS perspective, the mean PFS and OS durations calculated from the analysis were utilised in the estimation of the cost-effectiveness of B-FOLFOX vs FOLFOX in the 2nd line setting.

7.2 De novo economic evaluation(s)

In the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	Reference case	Section in 'Guide to the methods of technology appraisal'
Defining the decision problem	The scope developed by the institute	5.2.5 & 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 & 5.2.6
Perspective costs	NHS and Personal Social Services	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 to 5.2.12
Synthesis of evidence on outcomes	Bases in a systematic review	5.3
Measure of health	QALYs	5.4

effects		
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12

HRQL, health related quality of life; NHS, National Health Service; QALYs, quality-adjusted life years

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

As per the final scope of the STA, the regimens considered within this appraisal contain bevacizumab in combination with oxaliplatin. The safety and efficacy of bevacizumab has been examined in pivotal studies in combination with the following two oxaliplatin containing regimens:

- oxaliplatin in combination with leucovorin and 5-FU (FOLFOX)
- oxaliplatin in combination with capecitabine (XELOX)

It has been assumed that bevacizumab will be used in combination with FOLFOX and XELOX using the same doses, frequency and duration of use as observed in the NO16966 pivotal trial.

Bevacizumab is administered as an intravenous infusion of:

- 5 mg/kg of body weight given once every 2 weeks when added to the FOLFOX regimen.
- 7.5 mg/kg body weight given once every 3 weeks when added to the XELOX regimen.

The initial dose should be delivered over 90 minutes. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30-minutes.

Both FOLFOX-4 and FOLFOX-6 are believed to be used in the NHS; however the vast majority of patients in England and Wales receiving FOLFOX receive FOLFOX-6 (Expert Opinion). Both regimens contain the same component drugs in similar doses

per two week cycle, however FOLFOX-6 uses the modified de Gramont treatment schedule, which has a reduced number of drug administration episodes per cycle compared to FOLFOX-4. It is considered that FOLFOX-6 and FOLFOX-4 offer equivalent clinical outcomes.

The main body of clinical evidence for bevacizumab in combination with oxaliplatin in the first-line setting comes from the NO16966 pivotal trial. This trial investigated bevacizumab in combination with the FOLFOX-4 regimen. However, given the use of FOLFOX-6 is more typical of UK practice, the cost effectiveness of using bevacizumab in combination with this regimen has also been evaluated assuming equivalent clinical outcomes to that of bevacizumab in combination with FOLFOX-4.

From hereon bevacizumab in combination with XELOX will be abbreviated to B-XELOX and likewise bevacizumab in combination with FOLFOX-4 and FOLFOX-6 will be abbreviated to B-FOLFOX-6 and B-FOLFOX-6 respectively.

Table 20 through 22 below describe the interventions of interest and figure 13 illustrates this same information as a schema. It can be seen that delivery of the B-XELOX regimen is likely to consume less resources that the B-FOLFOX regimens due to its longer cycle length and thus few administration visits per months.

Table 20: B-XELOX treatment regimen as per NO16966 protocol

given every 21 days	Day 1 (Immediately after bevacizumab infusion)	Days 2 to 14	Days 15 to 21
Oxaliplatin Infusion over 120 minutes	130 mg/m2	-	
Capecitabine Oral therapy	*Days 1-14* Capecitabine 1000 mg/m^2 by mouth, twice daily, within 30 minutes of the end of breakfast and dinner. Capecitabine 1000 mg/m^2 by mouth, twice daily, within 30 minutes of the end of breakfast and dinner.		No Treatment

Table 21: B-FOLFOX-4 treatment regimen per the NO16966 protocol

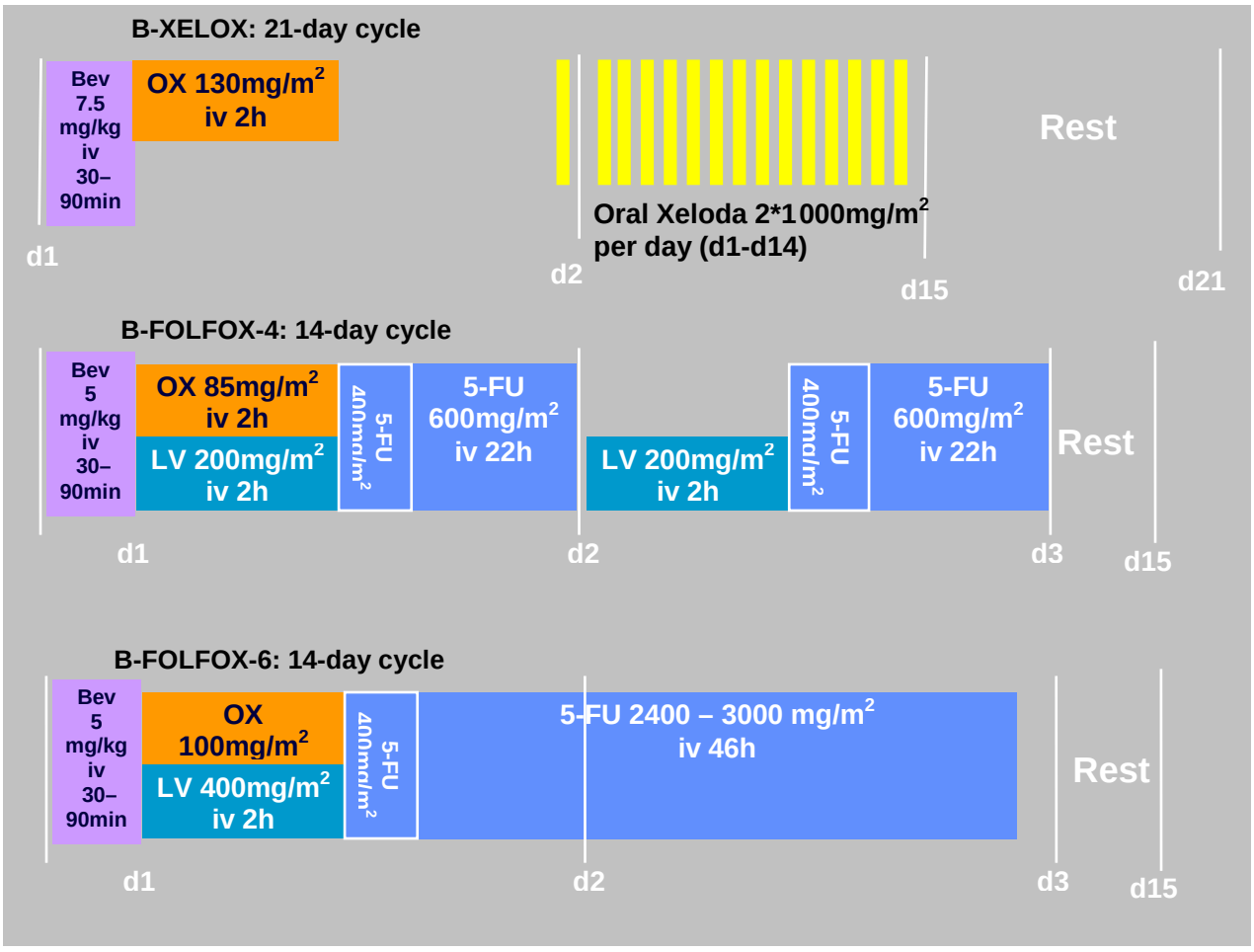
given every 14 days	Day 1 (Immediately after bevacizumab infusion)	Day 2
Oxaliplatin Infusion over 120 minutes	85 mg/m2	-
Folinic acid Infusion over 120 minutes	200 mg/m²	200 mg/m²
5-FU Bolus (over 2–4 minutes) followed by a 22-hour infusion	400 mg/m² bolus, followed by 22- hour continuous infusion of 600 mg/m²	400 mg/m² bolus, followed by 22-hour continuous infusion of 600 mg/m²

Table 22: B-FOLFOX-6 treatment regimen (FOLFOX-6 is the variant of the FOLFOX regimen typically used in the UK)

FOLFOX-4 chemotherapy given every 14 days	**Day 1 - 2 (Immediately after bevacizumab infusion)**
Oxaliplatin Infusion over 120 minutes	100 mg/m2 -
Folinic acid Infusion over 120 minutes	400 mg/m²
5-FU Bolus (over 2–4 minutes) followed by a 46-hour infusion	400 mg/m² bolus, followed by 26- hour continuous infusion of 2400 - 3000 mg/m²

A schema illustrating the administration schedules for both B-XELOX and B-FOLFOX-4 and B-FOLFOX-6 is shown below.

Figure 13: Schema of per protocol treatment schedule for regimens B-XELOX and B-FOLFOX



Concomitant treatments

There are no concomitant treatments required for treatment with B-FOLFOX or B-XELOX that are likely to have a meaningful impact on the cost effectiveness of these interventions.

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)
- the robustness and plausibility of the endpoint on which the rule is based
- whether the 'response' criteria defined in the rule can be reasonably achieved
- the appropriateness and robustness of the time at which response is measured
- whether the rule can be incorporated into routine clinical practice
- whether the rule is likely to predict those patients for whom the technology is particularly cost effective
- issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The economic analysis is based on the observed treatment duration in the NO16966 study to ensure that the cost of treatment match the clinical outcomes conferred from this expenditure.

The SmPC states that treatment of bevacizumab is to be continued until disease progression. In the NO16966 trial the average treatment duration was less than the time to progression. This was because treatment with bevacizumab was often stopped at the same time-point as the base chemotherapy was stopped. One can therefore only speculate as to the treatment effect of bevacizumab should it have been provided as per the SmPC recommendations.

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Bevacizumab has previously undergone a formal assessment by NICE for the treatment of patients with metastatic carcinoma of the colon or rectum (CRC); published in January 2007. This assessment related to the original marketing

authorization, which licensed bevacizumab in combination with IV 5FU/Folinic acid with or without irinotecan.

The most recent update to the bevacizumab marketing authorization for CRC, based upon the NO16966 phase III RCT, is now less prescriptive in the combination therapies bevacizumab may be combined with. Consequently the license now states "Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum".

As per the final scope of this Appraisal the economic evaluation did not attempt to update or present any further economic evidence in relation to the original metastatic colorectal bevacizumab license and concentrated exclusively on the new elements of the updated bevacizumab license. The population included in the analysis are patients with metastatic colorectal cancer for whom oxaliplatin-including chemotherapy regimens are suitable.

The cost effectiveness of bevacizumab in both the first and second line settings was assessed. The focus of the investigation however was on the use of bevacizumab in the first line setting for the following reason: Whilst the E3200 RCT clearly demonstrated the clinical benefits of adding bevacizumab to the FOLFOX regimen in the second-line setting, the dose of bevacizumab administered per cycle in E3200 was double of that used in the NO16966 study. Ball-park estimates of the ICER in the second-line setting (based on the "high dose") suggest that it would not be possible to demonstrate a case for bevacizumab in this setting and therefore a more detailed analysis has not been performed.

The patient cohort within the economic evaluation is assumed to have the same baseline characteristics as those observed in the NO16966 RCT and E3200 RCT for first- and second-line respectively. As these trials represented the pivotal studies supporting the licence amendment, it can be considered that the economic evaluation is reflective of the section of the licence indication evaluated. The baseline characteristics of these trials are detailed in Section 6.3.2 above.

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

As per the final scope analysis was not performed for any subgroups.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

Please see section 7.2.2.2 above.

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

For the first line analysis all patients enter the economic evaluation at the point of commencement of first-line treatment. Patients entered into the arm in the economic analysis as per the arm in which they were randomised in the NO16966 study. Patients remain in the model for the remainder of their life.

For the second-line analysis all patients enter the model at the point beginning treatment second-line.

7.2.3 Comparator technology

1.1.1.1 What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

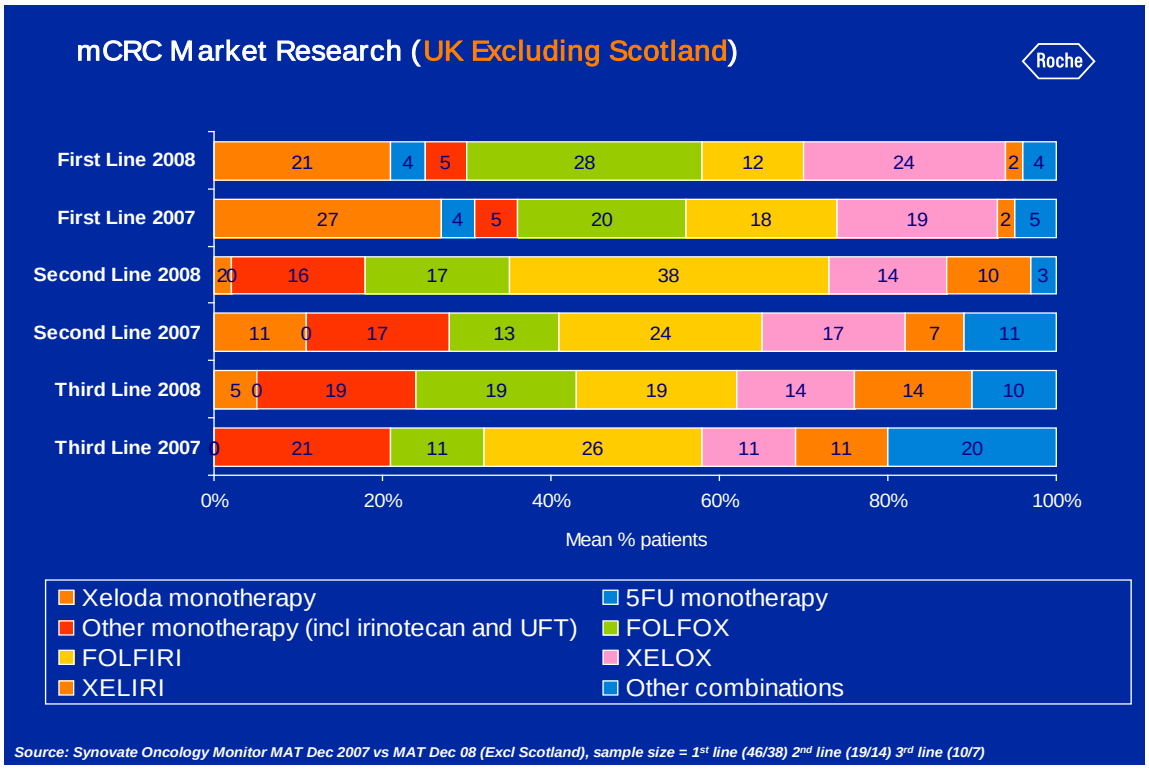
1.1.1.2

As discussed in section 2.2.2.1 the focus of the economic analysis was on first-line treatment. The inclusion criteria for comparators were as follows:

- The therapy is routinely used in the NHS (>10% usage)
- The therapy is within the final scope of the appraisal (i.e. oxaliplatin or irinotecan containing regimens without bevacizumab)

Therapies were considered to be used routinely if it was estimated, based on market research, that they were used to treat greater than 10% of mCRC patients that are treated with first-line chemotherapy in the NHS in England and Wales. The results of the market research are shown below in figure 14 below.

Figure 14: Estimated usage of chemotherapy by regimen and line in England and Wales in the NHS



Based on the criteria stated above the following regimens were considered appropriate comparators:

- FOLFOX
- XELOX
- FOLFIRI

FOLFOX is estimated to be the most used regimen in the NHS in this patient population. XELOX is the next most used regimen. A minority of patients (12%) receive FOLFIRI.

There are two main treatment schedules used to deliver FOLFOX and FOLFIRI regimens, the de Gramont schedule and the modified de Gramont schedule. Clinical experts indicated that the vast majority of FOLFOX / FOLFIRI in the UK is based on modified de Gramont schedule (Expert Opinion). The main clinical data on which this submission is based the NO16966 study used the de Gramont regimen. Given it's predominance in the UK, an analysis based on the modified de Gramont schedule has also been performed.

Due to a lack of direct (head to head) evidence, results from a comprehensive independent mixed treatment comparison by Golfinoupoulos et al (discussed in section 6.6) were used for evaluating the relative efficacy of FOLFIRI compared to the other interventions.

7.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

The economic analysis reflects the perspective of the NHS and Personal Social Services.

7.2.5 Time horizon

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between the technologies being compared.

What time horizon was used in the analysis, and what was the justification for this choice?

An 8 year time horizon was used; equivalent to life-time time horizon in the population of interest. Virtually all patients within the economic model were followed to death (only <0.1% of the cohort are estimated to survive past this period).

7.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

7.2.6.1 Please provide the following.

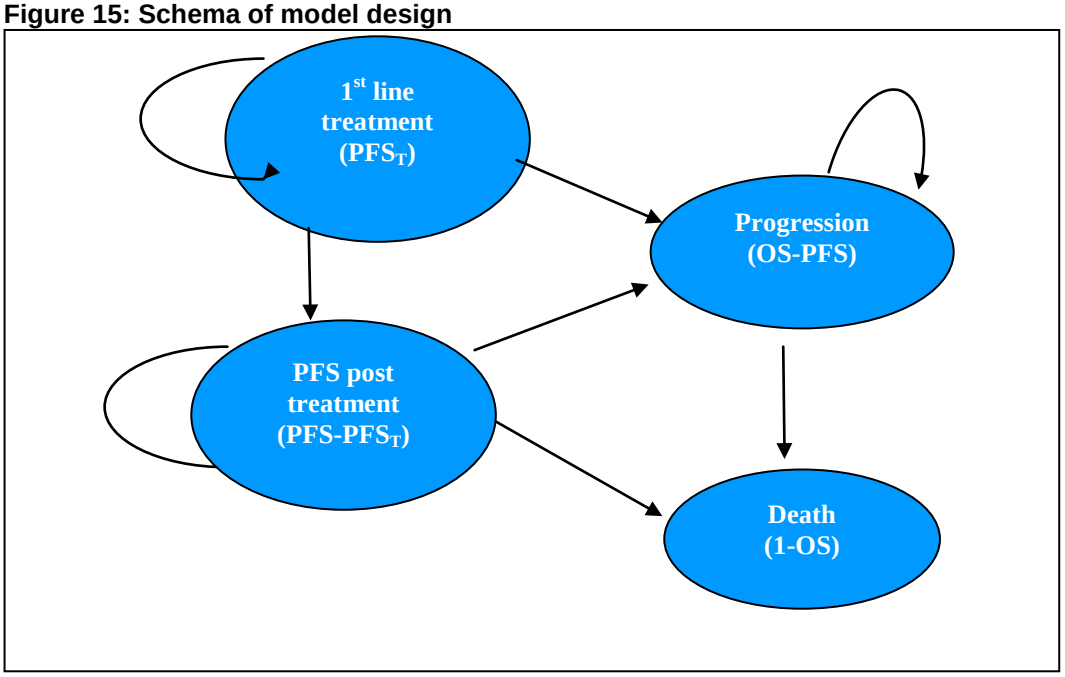
- A description of the model type.

- A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
- A list of all variables that includes their value, range (distribution) and source.
- A separate list of all assumptions and a justification for each assumption.

Model Structure (1st line analysis)

A 4 stage, Excel based, area under the curve model was designed to estimate the disease progression of metastatic colorectal cancer patients and the subsequent total direct costs and QALYs for each intervention. The model had a cycle length equal to one month. The definition of the 4 selected health states were aligned with the respective phase III RCT (NO16966). 3 of the health states are typical of previous economic evaluations of metastatic oncology interventions, progression-free survival (PFS), progressive disease (PD) and death. However for this analysis the PFS health state was divided in to two separate health states, First-line treatment (PFS_T) and PFS after treatment cessation (PFS_{PT}). This was done in order to more transparently capture the difference in costs and utilities experienced during treatment and after treatment whilst in PFS.

Figure 15: Schema of model design



All patients were assumed to start in the PFS_T health state, consistent with the NO16966 study. Kaplan-Meier data from the NO16966 RCT for time to cessation of first-line treatment was used to estimate the mean duration patients spent in the PFS_T health state. Due to the completeness of these Kaplan-Meier data no extrapolation was require for this health state.

The Kaplan-Meier data from the NO16966 RCT for PFS, and overall survival (OS) were extrapolated using parametric survival analysis in order to estimate the

proportion of patients in the PFS (PFS_T + PFS_{PT}) and death health states for the expected lifetime of the patient. The most appropriate parametric function was selected following extensive statistical analysis of each function's goodness of fit, further details on these extrapolation methods are provided in section 7.2.6.8.

The proportion of patients in PFS was derived directly from the extrapolated PFS curve for each cycle of the model. The proportion of patients in the post treatment health state was calculated as the residual of PFS and the PFS_T health states (1-(PFS+PFS_T). Similarly the proportion of patients who were in the health state of death was also derived directly from the extrapolated overall survival curves and calculated as [1-OS]. The proportion of patients within the progressive disease health state was then calculated as the residual of the PFS and Death health states (1 – [PFS+death]). Parametric extrapolation of the Kaplan-Meier curves allowed the proportions of patients in each health state to be estimated for the period beyond the trial follow-up, where no data from the RCT on disease progression or survival is known.

Utility scores were applied to each health state in each cycle of the model to adjust for the patient's health related quality of life. Direct healthcare costs associated with each health state (excluding death) were also applied in each cycle of the model along with the standard discount rate (3.5% pa) for both costs and benefits. A half-cycle adjustment was applied in the model to account for the fact that not all costs and outcomes occur at the end of each cycle. The model was then able to produce estimates of each oxaliplatin-based intervention's life expectancy, QALYs and direct NHS costs for each intervention along with the subsequent ICER.

Hazard ratios for PFS and OS derived from the mixed treatment comparison were applied to the FOLFOX PFS and OS survival curves to estimate the time spent in each health state for patients receiving FOLFIRI.

Below is a table summarising the model parameters and values used in the model.

Table 23: Model Parameters and Values

Model Variable	Value	Source
Area under the curve		
1st line treatment (PFS_T)	Proportion of patients on treatment at month t out of proportion of patients in PFS at month t taken from each regimen and applied to the PFS curve based on the pooled ITT analysis as described in section 6.4.1.1 The same ratio of treatment duration to PFS was used in the	NO16966

	FOLFIRI comparison as observed in FOLFOX arm of NO16966.	
PFS	KM curves until median follow-up. Exponential extrapolation for the remainder of the PFS period based on the mean risk of progression between months 13-28.	NO16966
Progression to Death (Progressive Disease)	1-(PFS+OS)	NO16966
OS	KM curves until the median of follow-up (28 months) Weibull extrapolation of trial data for remainder of the OS period.	NO16966
Costs		
Supportive-care costs		
Monthly PFS health state supportive care • Consultation • Bloods • CT scan	£174 when on treatment £108 when off treatment One consultation visit per month when on treatment reducing to every 2 months when not on treatment Bloods every treatment cycle. CT scan every 3 months	Expert Opinion; NHS reference costs, 2007/8 ; RCC MTA, 2008
Monthly PD costs	£600	Tappenden 2007
Cycles per month		
5-FU-based regimens	1.83	Mean cycles per month on treatment in NO16966
Capecitabine-based regiments	1.31	
Drug acquisition costs per treatment cycle†		
Bevacizumab	<u>B-XELOX: £1,200</u> <u>B-FOLFOX: £800</u>	APAS

5-FU	£0.0128/mg * observed trial dose per cycle.	BNF57 ; NO16966
Leucovorin	£0.301/mg * observed trial dose per cycle	BNF57 ; NO16966
Oxaliplatin	£3.135/mg* observed trial dose per cycle	BNF57 ; NO16966
Capecitabine	£0.004917/mg* observed trial dose per cycle	BNF57 ; NO16966
Irinotecan	£1.302/mg* protocol dose * RDI (93%)	BNF57 ; Douillard 2000
Drug acquisition costs per month	Per cycle cost * observed mean number of cycles per month in trial	NO16966
Drug administration and pharmacy costs per cycle (per month cost[T])		
B-XELOX	£444 (£581)	NO16966; ref cost 2007/8 (see section 7.2.1 for more details)
B-FOLFOX-6	£600 (£1,100)	
B-FOLFOX-4	£954 (£1,749)	
B-FOLFOX-4 inpatient	£988 (£1,812)	
XELOX	£402 (£526)	
FOLFOX-6	£558 (£1,024)	
FOLFOX-4	£912 (£1,673)	
FOLFOX-4 inpatient	£946 (£1,735)	
Drug administration costs per month	Per cycle cost * observed mean number of cycles per month in trial	NO16966
Utilities		
PFS_T	0.79	NICE first-line Cetuximab STA (modified based on Expert Opinion and Petrou *et al* 2005)
PFS_{PT}	0.77	NICE first-line Cetuximab STA
2nd line PFS (2nd line analysis only)	0.73	
Post progression	0.67	
Discount rates		
Costs	3.5%	Guide to Methods, NICE
QALYs	3.5%	Guide to Methods, NICE

[T]per cycle costs multiplied by observed mean number of cycles in the NO16966. (see section 7.2.1)

The calculation of parameter estimates as well as further detail on the references is provided in the appropriate sections below. The assumed ranges for each model parameter are listed in Appendix E3 when describing the probabilistic sensitivity analysis (PSA). Further details on the calculation of costs are provided in Section 7.2.9.

Main Assumptions in the economic model

The XELOX and FOLFOX arms of the NO16966 study are equivalent in terms of efficacy and the B-XELOX and B-FOLFOX arms of the NO16966 are equivalent in term of efficacy. The rational for estimating the treatment effect of bevacizumab by comparing the pooled bevacizumab + chemotherapy arms with the pooled chemotherapy alone arms in the NO16966 study is described in section 6.4.1 above.

Second- and third-line treatment costs post progression are equivalent across all the interventions / comparators. The proportion and mix of anti-cancer treatments given post progression were very similar across all of the treatment arms of the NO16966 RCT (see Appendix E5). It was therefore assumed that there was no difference between the arms in terms of second- and third-line treatment costs and thus these costs have been excluded from the analysis. Monthly supportive care costs were applied to the PD health state and sensitivity to variation in this monthly cost was explored in the sensitivity analysis.

The choice of treatment schedule between de Gramont and modified de Gramont does not impact the clinical outcomes of either FOLFOX or FOLFIRI.

The cost of adverse events for FOLFIRI was assumed to be equivalent to that of FOLFOX. Adverse event costs are not a major driver of cost effectiveness in the model (see sensitivity analysis section 7.3.3). Whilst it is recognised that there is a different toxicity profile between the FOLFOX and FOLFIRI regimens it was not considered that these differences in cost would materially affect the results of the analysis.

Quality of life whilst in each health state is not affected by which regimen a patient is treated with. The comprehensive safety data collected in study NO16966 and elsewhere, that has been meta-analysed by Cao et al (2009), demonstrated that B-XELOX and B-FOLFOX have similar tolerability to FOLFOX and XELOX.

Quality of life is assumed to be adversely affected by treatment side effects whilst on treatment. Hence patients are assumed to have a slightly higher utility in the period of time in-between stopping treatment and progression. The OPTIMOX1 (Bidard F et al 2008) trial investigated intermittent treatment with FOLFOX for the purpose of reducing the impact that chemotherapy has on quality of life. The fact that this trial was conducted supports the belief that quality of life is affected by the side-effects of oxaliplatin base chemotherapy. The sensitivity of the ICER to changes in the assumed utility value for the PFS_{PT} health state was explored in the one-way sensitivity analysis.

It was assumed that there is no wastage of drugs.

Bevacizumab is supplied, as part of APAS, at a fixed price per cycle, therefore wastage in not of relevance to the estimation of the acquisition cost of bevacizumab per patient. It has been assumed that the other drugs in the regimen are able to be compounded so that any wastage would be negligible. This assumption potentially favours the comparator treatments as oxaliplatin is provided free of charge as part of the APAS.

7.2.6.2 Why was this particular type of model used?

Some form of modelling exercise was required as not all patients were followed until death therefore extrapolation of the clinical trial data was required for PFS and OS. The median follow-up period of the NO16966 study on which the analysis is based was sufficiently long to follow the majority of patients until disease progression and then until death. Given survival time did not greatly exceed the time frame of the main clinical trial an area under the curve model was considered appropriate.

7.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure of stratifying the clinical outcomes of oncology patients into progression-free, progression, and death is common practice in the economic evaluation of oncology and is consistent with previous health technology assessment of therapies for first-line mCRC. The health states align with one of the key objectives of treatment within this disease area: to place a patient into a progression-free health state for the longest period possible. Furthermore, the main outcomes of the clinical trial could be stratified into one of these 3 heath states: progression-free survival, progressed patients and death. Given that there was a substantial gap between the time when patients stopped first-line treatment and when they progressed a forth health state was added that split the progression-free health state into on treatment and post-treatment phases. This was done in order to more transparently capture the difference in costs and utilities experienced during treatment and after treatment whilst in PFS.

7.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The model was structured around the NO16966 RCT. This trial provided the proportion of time a patient spent in each of the health states before death. Hazard ratios from the mixed treatment comparison (described in Section 6.6) were applied to the FOLFOX survival curves to estimate the costs and outcomes of the FOLFIRI regimens.

7.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The 4 health states within the model capture all conditions relevant to the decision problem.

7.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The cycle length of the model is monthly. Clinical assessment is not performed on a more regular basis than every month. Therefore it is reasonable to assume that costs or clinical outcomes would not change on a more frequent basis than every month.

7.2.6.7 Was a half-cycle correction used in the model? If not, why not?

A half-cycle correction was applied to the model.

7.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

For the purposes of survival analysis the intention to treat (ITT) population from the NO16966 study was utilised. Despite there being a relatively mature follow-up of patient outcomes (median of 28 months) at the time of the latest data cut there was still a proportion of patients that were still alive or who had not progressed. 15.0% and 9.3% of patients remained in PFS for the bevacizumab+chemotherapy and chemotherapy-alone arms respectively, and 39.9% of patients were alive in the bevacizumab+chemotherapy arms and 27.6% of patients were still alive in the chemotherapy alone arms. Consequently as is common practice within economic evaluation a parametric extrapolation of the survival data was performed in order to estimate the longer term outcomes for those patients not having experienced the endpoints of interest within the study.

The parameters for the endpoints PFS and OS, under the assumption of a parametric survival function, were estimated using the clinical data. Gompertz, Weibull, Log Logistic, Log Normal and Exponential survival functions were estimated based on the data and then assessed for goodness of fit. To assess goodness of fit the Akaike (AIC) and Bayesian Information Criteria (BIC) statistics were utilised along with a graphical inspection the fit of the data before selecting the most appropriate curve for the final model. The data from the clinical study was truncated at 28 months (median overall survival follow-up) to overcome the large uncertainty in the tails of the survival curves and the imbalance in the length of follow-up between patients treated with bevacizumab and those with chemotherapy alone prior to fitting the extrapolated curves.

Extrapolation for treatment duration (i.e. estimating time in the PFS_T health state) was not required due to the completeness of the time to treatment cessation Kaplan-Meier curves (see figure 18 section 7.6.2)

Progression Free Survival

Extrapolation of the progression free data was carried out under the assumption that the data followed a parametric model structure. The parameters were estimated using the available clinical data.

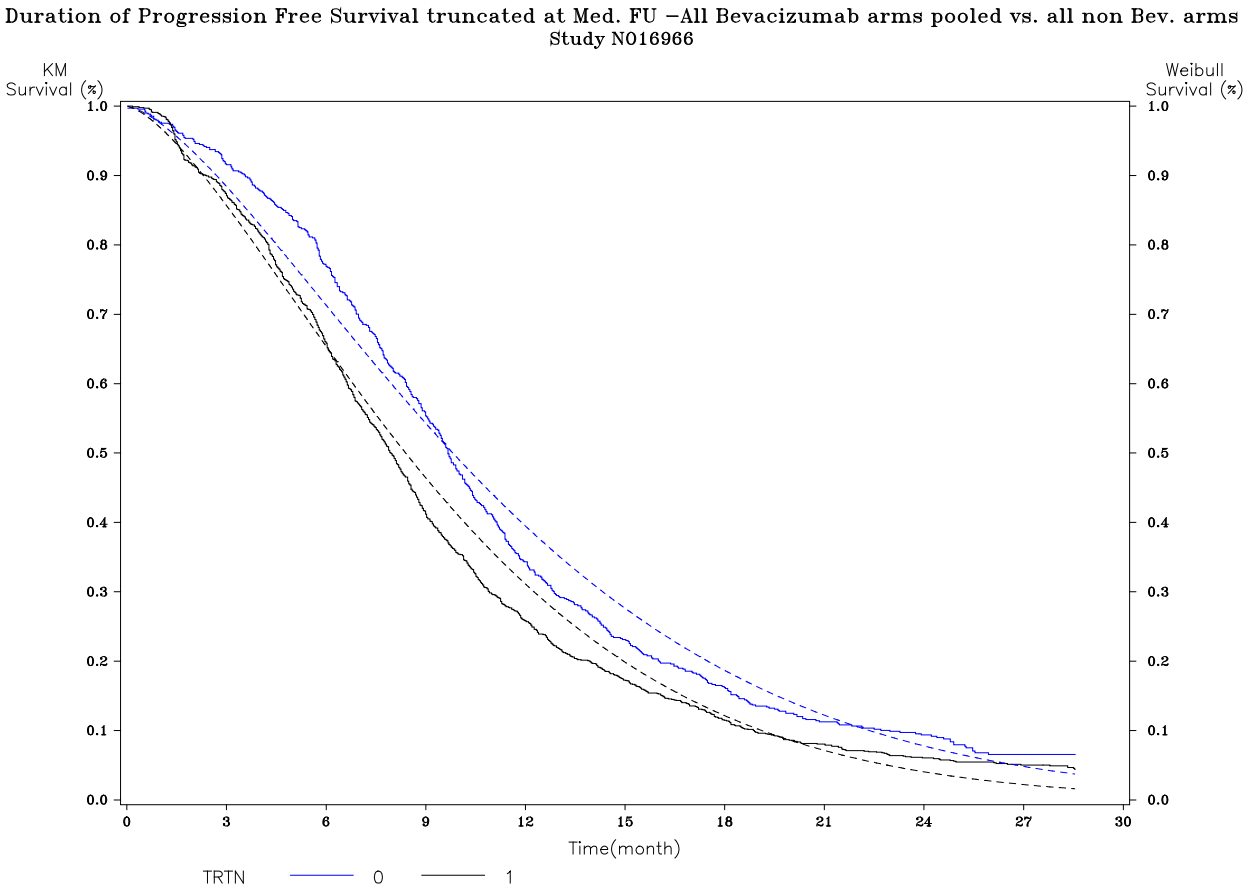
Table 24: Summary of Parametric Functions' Goodness of Fit for PFS

Parametric Model	**AIC**	**BIC**
Exponential	-2611.33	-2613.14
Log Logistic	-2395.35	--2398.97
Log Normal	-2467.13	-2470.75
Weibull	-2432.55	-2436.16
Gompertz	NC	NC

NC = not calculated because not available in current tools. The maximum likelihood is not performed in Proc NLIN (not available in SAS)

The parametric function with the lowest AIC and BIC value and subsequently representing the best statistical goodness of fit was the log logistic function. However, graphical examination ruled the log logistic function out as it seemed to severely over-estimate the tail of the survival curves. This was not the case with the Weibull function which provided next best statistical fit after the log-logistic distribution though visual inspection of the Weibull curve also suggested a poor fit (see Figure 16 below).

Figure 16: Extrapolated Progression-Free Survival curves of Oxaliplatin based chemotherapy plus Bevacizumab versus Oxaliplatin based chemotherapy alone using Weibull Survival Function



Source: SAS v8.2 ducournp $HOME/cd10743a.pbe/i16966m.pbe/modldth.sas 22JUN2009 15:22

Key: Blue: (B-XELOX / B-FOLFOX) ; Black: (XELOX+-P / FOLFOX+-P) ; solid lines represent the KM curves ; dashed lines represent the parametric curves.

Finally, given the completeness of the PFS Kaplan-Meier curves it was decided to use the Kaplan-Meier curve up until the median follow up (28 months) and extrapolate from this time-point on. As can be seen from figure 16 above the PFS curves appeared to go through 3 phases, from month 0 to 5, months 6 to 12 and month 13 on. Therefore the extrapolation for the remainder of each of the curves was based on an exponential survival function with a hazard equivalent to that of the average hazard in the last phase of the curve.

The extrapolated curves as used in the base case are shown below in Figure 19 at the bottom of this section. The affect on the ICER of using alternative curves is presented as part of the sensitivity analysis.

Overall Survival

As per the PFS extrapolation, all available parametric functions were assessed for their fit to the OS data with the Weibull function being selected as the best fit to model the data beyond the clinical follow up. The Weibull function was not only found to have a good statistical fit to the data but was consistent with the proportional hazard assumption of the Kaplan-Meier model. The concept of proportional hazards for the purpose of the economic model is that the shape parameter is the same for both treatment arms. The goodness of fit results are presented in the table below:

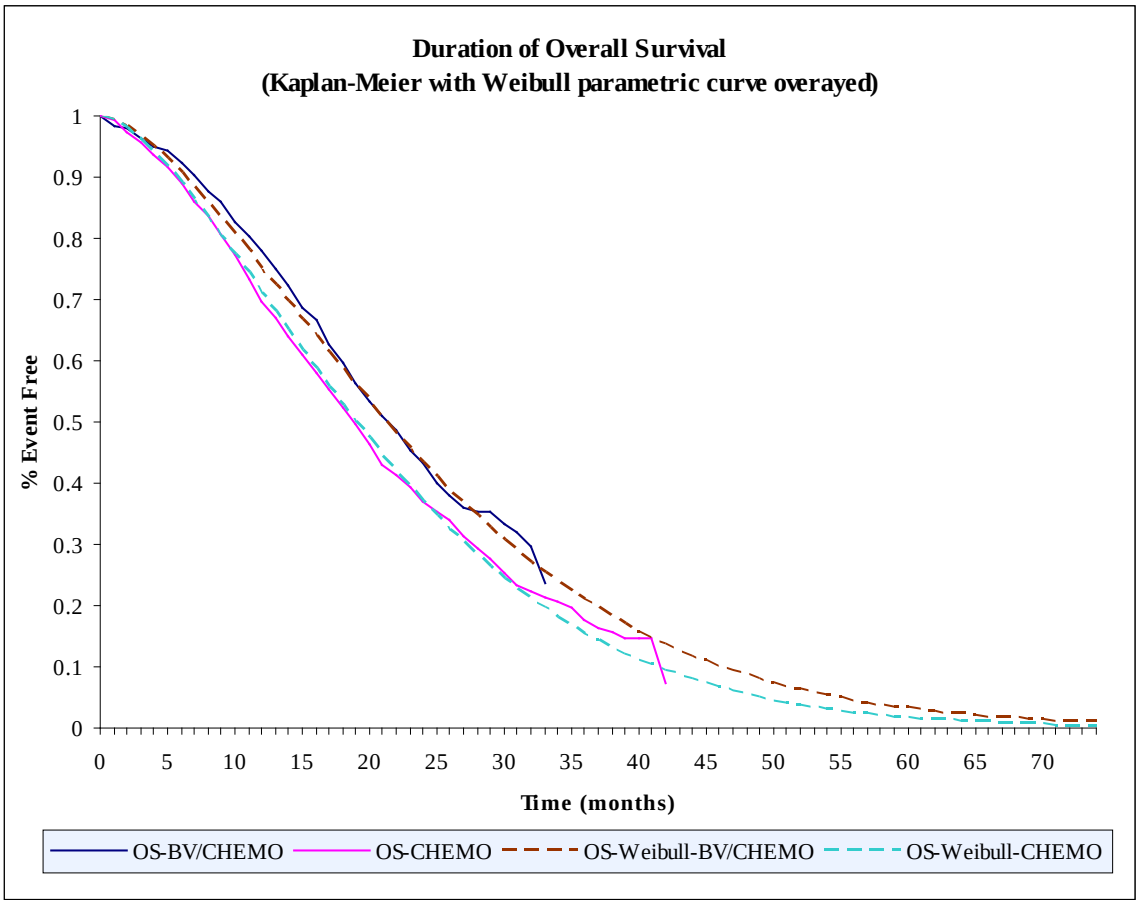
Figure 17: Summary of Parametric Functions' Goodness of Fit for OS

Parametric Model	AIC	BIC
Exponential	-2453.88	-2455.69
Log Logistic	-2338.63	-2342.25
Log Normal	-2396.03	-2399.65
Weibull	-2325.82	-2322.20
Gompertz	NC	NC

NC = not calculated because not available in current tools. The maximum likelihood is not performed in Proc NLIN (not available in SAS).

Whilst the Weibull curve provided the best statistical fit, when visually comparing it with the Kaplan-Meier OS curves it did not appear to fit the first section of the curve well (see Figure 18 below). Therefore as with PFS it was decided to use the Kaplan-Meier data up until the end of follow-up and then extrapolate the curve from this time-point on using the Weibull function with the parameters shown above. By using these parameters a treatment effect is assumed to continue beyond median follow-up. The effect on the ICER to changes in this assumption was explored in the sensitivity analysis.

Figure 18: Extrapolated overall survival curves of oxaliplatin-based chemotherapy plus bevacizumab versus oxaliplatin-based chemotherapy alone using the Weibull survival function



Note: Weibull parameters were estimated using data up until median follow-up (28 months)

Extrapolation of PFS and OS for FOLFIRI

A constant hazard ratio (taken from the mixed treatment comparison) was applied to the extrapolated FOLFOX PFS and OS survival curves to derive the survival curves for FOLFIRI.

Parameter estimates for the Weibull function in OS and PFS are shown in the table below.

Table 25: Weibull Parameter Estimates for OS and PFS by Treatment Arm

Efficacy Endpoint	Bevacizumab + Chemotherapy	Chemotherapy alone
Overall Survival (OS)		
Lambda	0.005869	0.006993
Gamma	1.547269	1.547269
Progression Free Survival (PFS)		
Lambda	0.024792	0.031139
Gamma	1.458364	1.458364

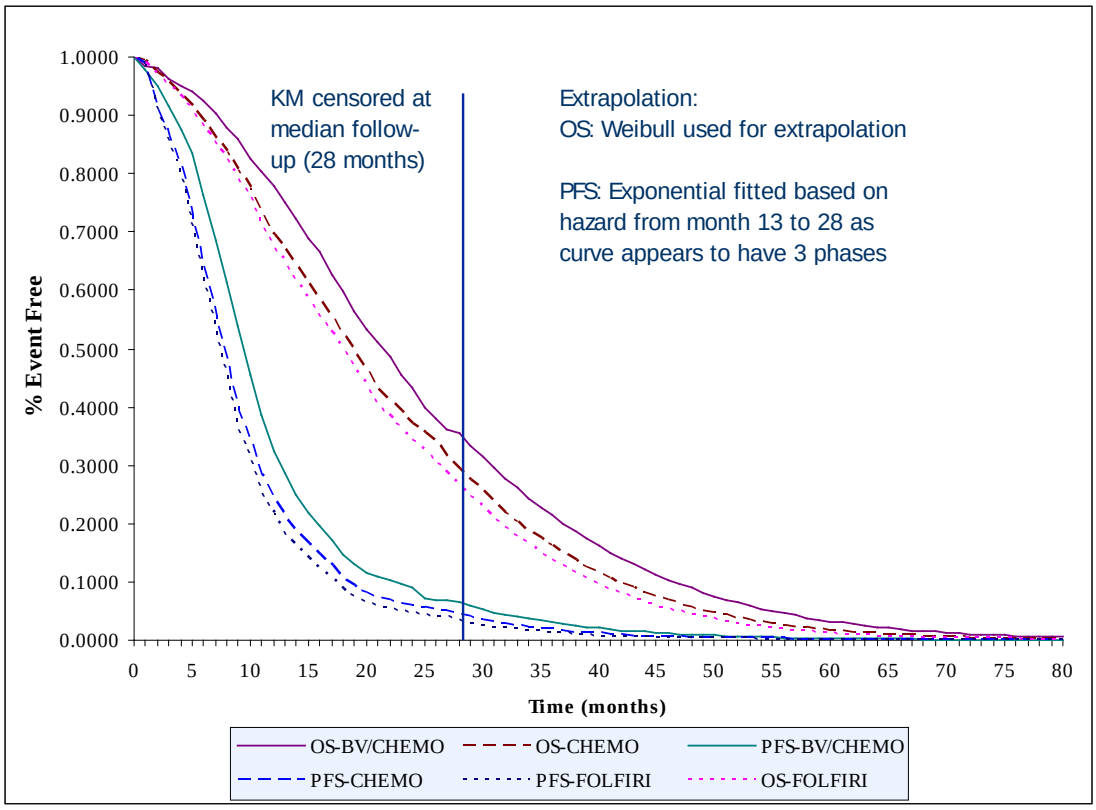
The PFS Weibull survival function is defined as

$$\text{with } \lambda = \exp\left(\frac{-(\mu+\delta)}{\sigma}\right) \text{ and } \gamma = \frac{1}{\sigma}$$

and δ representing the treatment covariate and the model μ intercept.

$$S(t) = \exp(-\lambda t^{\gamma}) \quad \text{with } \lambda = \exp\left(\frac{-(\mu+\delta)}{\sigma}\right) \text{ and } \gamma = \frac{1}{\sigma}$$

Figure 19: Extrapolated Survival Curves used in the Base Case Analysis



Nb: KM curves for FOLFIRI were derived from applying the hazard rations in the mixed treatment comparison to the FOLFOX KM from the NO16966 study

7.2.6.9 b) Non-model-based economic evaluations

7.2.6.10 Was the evaluation based on patient-level economic data from a clinical trial or trials?

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.6.11 Provide details of the clinical trial, including the rationale for its selection.

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.6.12 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.6.13 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.6.14 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not Applicable. Only model-based economic evaluations were performed for this submission.

7.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided

7.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

For first-line comparisons of the oxaliplatin regimens an “area under the curve” model design was utilised. The risk for disease progression and death was derived from the NO16966 RCT. The risk of disease progression for the oxaliplatin-based therapies was based on the Kaplan-Meier analysis until the median follow-up after which time-point the risk of disease progression was based on the extrapolation of the survival data as described in section 7.2.6.8 above.

Head-to-head clinical trial data was not identified comparing the bevacizumab containing interventions of interest with FOLFIRI. In a previous NICE appraisal the Appraisal Committee concluded that it would not differentiate between these two drugs in terms of clinical effectiveness [section 4.3.5 FAD TA93]. Subsequent to this guidance being published a comprehensive independent mixed treatment comparison (see section 6.6) was performed, which contained multiple studies either directly or indirectly comparing 5-FU in combination with oxaliplatin versus 5-FU in combination with irinotecan. The hazard ratios for PFS and OS from this analysis applied to survival curves of FOLFOX to estimate the survival curves for the FOLFIRI arm of the model.

For the second-line comparison of the mean time in PFS and OS was taken from the cost effective analysis of E3200 performed by Shiroiwa et al 2007.

7.2.7.2 How were the relative risks of disease progression estimated?

Please see section 7.2.7.1 above.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The health states of, first-line treatment, progression free survival post treatment, and ”progressed” were linked to the final outcome of QALYs in the model. The utility scores were informed by estimates from the literature, and in respect to progression free survival post treatment, adjusted based upon expert opinion (see Section 7.2.8.3).

7.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The cost of treating adverse events of grade 3 and above was included in the analysis. The details of how these costs were estimated and applied in the model are provided in section 7.2.9.1

Any disutility of receiving first-line chemotherapy is assumed to have been captured in the utility value for the first-line treatment health state (PFS_T). It was assumed that no differential in monthly utility value between the arms existed given that the comprehensive safety data collected in NO16966 and elsewhere, that was meta-analysed by Cao *et al* (2009), demonstrated that B-XELOX and B-FOLFOX has similar tolerability to FOLFOX and XELOX alone.

7.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was used to inform the modification of the PFS_T utility value to estimate utility value for the PFS post treatment (PFS_{PT}) health state. Additionally expert opinion was used to inform the following clinical practice assumptions:

- The percentage of patients in the UK that have a central venous access devise (CVAD) installed.
- The percentage of patients that received the 5-FU infusions via an ambulatory pump as opposed to receiving these infusions via a hospital based pump as an inpatient.
- Frequency of district nurse visits to disconnect the ambulatory pump and flush the CVAD.
- Frequency of consultations during PFS
- Type and frequency of tests during PFS
- Proportion of patients requiring NHS funded transport to attend hospital.
- The proportion of patient not suitable for capecitabine based therapy
- The proportion of patients receiving homecare

Summary feedback on the model structure and clinical assumptions was obtained during a Roche advisory board meeting attended by 8 clinicians highly experienced in the treatment of mCRC. Further follow-up telephone and face-to-face interviews were conducted with 3 of these experts where each expert was asked to provide information and estimates for each of the assumptions listed above. A list of attendees of the meeting and the 3 experts engaged in the estimation of the relevant parameter is listed in Appendix E2.

Uncertainty around these clinical practice assumptions was explored in the one-way sensitivity analysis.

7.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

All assumptions relating to clinical evidence have been previously described in Section 7.2.6.1

7.2.8 Measurement and valuation of health effects

The value of health effects should be expressed in terms of QALYs for the appropriate time horizon. For the reference case, the measurement of changes in HRQL should be reported directly from patients and the value of changes in patients' HRQL (that is, utilities) should be based on public preferences using a choice-based method. The EQ-5D is the preferred measure of HRQL in adults. The methods to elicit EQ-5D utility values should be fully described. When EQ-5D data are not available or are inappropriate for the condition or effects of treatment, the valuation methods should be fully described and comparable to those used for the EQ-5D. Data collected using condition-specific, preference-based measures may be presented in separate analyses. The use of utility estimates from published literature must be supported by evidence that demonstrates that they have been identified and selected systematically.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.8.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

For the purpose of the economic analysis health effects have been expressed using QALY's

7.2.8.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The health effect associated with the first-line treatment, PFS post treatment and progressed states were measured via survival analysis and valued via utility scores. This allowed for different health benefits to be calculated for patients in the intervention and comparator arms by taking into account the difference in life expectancy and the duration of time spent in each of these states.

7.2.8.3 How were health effects measured and valued? Consideration should be given to all of the following:

- State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.
- Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.
- Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.
- How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?
- Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.
- Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.

No quality of life data was captured in the NO16966 study and therefore utility values were sourced from the literature.

Two potential sources for relevant utility values were identified in the literature. The first reported utility values of 0.8 and 0.6 for PFS and progression respectively. These had been used in the previous NICE appraisal for bevacizumab for the treatment of first-line mCRC. However these values, from Ramsey et al, were not elicited using the methods stated in the NICE reference case as they were based on 173 subjects with CRC (various Preferences elicited using the Health Utilities Index Mark 3 stages) sampled from US SEER (HUI3) database completed the survey.

The second set of utility values was sourced from the recent NICE appraisal of cetuximab in the first line treatment of mCRC (Cetuximab STA) The PFS utility values represented the mean utility derived from EQ-5D results from 42 patients taken from both arms of the Crystal study. The Crystal study was a PhIII randomised controlled trial comparing cetuximab in combination with FOLFIRI with FOLFIRI alone in the 1st line treatment for mCRC. EQ-5D scores were recorded at weeks 8, 16, 24, 32, and 40 of this trial.

Experts (Expert Opinion) indicated that patients receiving bevacizumab would expect to report higher utility values than that of patients treated with cetuximab for the first weeks of treatment after which point the utility values were considered to be most likely equivalent. The affect on the ICER of changes to the utility values used in the analysis were explored in the sensitivity analysis.

The utility value of the progressed health state was also sourced from the aforementioned cetuximab technology appraisal. This value was elicited using HUI from patients enrolled in a study investigating the use of cetuximab for the third-line treatment of mCRC.

Based discussion during the Roche advisory board (list of attendees Appendix E2) it was deemed that utility values in the PFS post treatment health state would be higher than that of patients receiving first-line treatment given that patients' disease is stable at this point and that they would no longer be experiencing the adverse effects of chemotherapy treatment. The value used for this health state was taken from EQ-5D data from the general UK population. (see table below)

Table 26: EQ-5D utility scores reported for the general population (Petrou 2005)

Age	Overall utility score
16-24	0.904
25-34	0.907
35-44	0.882
45-54	0.847
55-64	0.789
65-74	0.778
>75	0.724

Table 27: Utility values used in base case analysis

Heath state	Utility weight	Source	Comments and assumptions
PFS_T	0.77	Cetuximab STA	UK EQ-5D data based on 42 patients. 0.77 is derived as an average of all EQ-5D completed responses over the study period (baseline to week 40)*
PFS_{PT}	0.79	1. Expert Opinion 2. Petrou	It was assumed that patients in PFS no longer receiving chemotherapy would experience higher quality of life to patients on 1st line treatment and that their utility would be equivalent to individual in the general UK population aged between 55 and 64 (median age in the NO16966 RCT

			was 60)
2nd line PFS	0.73	Cetuximab STA	As per the assumption made by Merck in the recent NICE appraisal of cetuximab 1st line, 2nd line utilities were assumed to be equivalent to the average of the 1st and 3rd line utility values. This value was only used in the 2nd line analysis of bevacizumab
PD	0.68	Cetuximab STA	Utility weights are measured in the trial using the HUI. Utilities did not rapidly deteriorate over the period of 0-24 weeks in 3rd line, and therefore the average was assumed until death. * For the 1st line analysis of bevacizumab this utility value was assumed to apply from progression on first line till death.

*Verbatim from source

7.2.8.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

No

7.2.8.5 Were any health effects excluded from the analysis? If so, why were they excluded?

The effect of adverse events upon health benefit and quality of life was excluded from the evaluation for the reasons described in Section 7.2.7.4.

7.2.9 Resource identification, measurement and valuation

For the reference case, costs should relate to resources that are under the control of the NHS and PSS when differential effects on costs between the technologies under comparison are possible. These resources should be valued using the prices

relevant to the NHS and PSS. Evidence should be presented to demonstrate that resource use and cost data have been identified systematically.

Some technologies may have a substantial impact on the costs (or cost savings) to other government bodies. In these exceptional circumstances, costs to other government bodies may be included if this has been specifically agreed with the Department of Health, usually before referral of the topic. When non-reference-case analyses include these broader costs, explicit methods of valuation are required. In all cases, these costs should be reported separately from NHS/PSS costs. These costs should not be combined into an incremental cost-effectiveness ratio (ICER; where the QALY is the outcome measure of interest).

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

7.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

1) Drug acquisition costs
2) Drug administration costs
    a) Pharmacy preparation and dispensing
    b) Administration day cases appointments
    c) District nurse visits
    d) Acquisition cost of ambulatory pumps
    e) Inpatient stays for treatment (for small minority of patients – 5%)
3) Monitoring
    a) Face to Face consultations
    b) CT scans
    c) Blood tests
4) Installation and replacement of central venous access devices (CVADs)
5) Treatment of Adverse Events
6) Supportive care costs post progression in first line

Overview of methods used for estimating costs per patient in the first-line analysis

Monthly costs for drug acquisition, pharmacy, drug administration, and monitoring were calculated as per treatment cycle costs multiplied by the average number of cycles per month as observed in NO16966. These monthly costs were then applied to the monthly model cycles to estimate the mean resource use per patient for each health state.

Kaplan-Meier survival analysis was used to calculate the mean treatment duration (i.e. time spent in the PFS_T health state) based on the time from first dose to the time until cessation of treatment as recorded in the NO16966.

Average Adverse event and CVAD costs per patient were applied to month one of the PFS_T health state and thus no discounting was applied.

The monthly drug acquisition cost of bevacizumab was only applied to the first 12 model cycles of the PFS_T health state to account for the 12 month price cap available through the Avastin Patient Access Scheme (APAS).

Given the very similar proportion of patients that received each of the post protocol treatments recorded in the NO16966 study (see appendix E5), it was assumed there were no differences in costs for second- and third-line treatment between the different intervention/comparators. Hence no cost for second- and third-line treatments has been applied in the model. Instead a monthly supportive care cost of £600 was applied for each of the interventions for the duration of post progression survival.

Overview of methods used for estimating costs per patient in the 2nd line analysis

For the 2nd line analysis, drug acquisition, administration and pharmacy per cycle costs taken from the first-line analysis were multiplied by the median number of treatment cycles reported in the E3200 study paper to estimate total treatment costs.

Monthly supportive care costs for PFS and PD (taken from the first-line analysis) were multiplied by the mean time in PFS and PD respectively.

Adverse events, third-line treatment and CVAD costs were not included in the analysis nor were the costs discounted given both that this was an exploratory analysis and that these elements were not expected to be the main drivers of the model.

Drug acquisition costs per cycle

Drug Acquisition unit costs

Bevacizumab is costed at the fixed per cycle price through the APAS. This is £800 and £1200 per 2 weekly and 3 weekly cycles respectively.

All other drug acquisition costs were taken from the most recent version of the BNF (BNF57) as summarised below, with the lowest cost generic version selected where both branded and generic presentations were available. Where the cost per mg differed depending on the vial size the weighted average price per mg was used. A full list of drug prices is included in Appendix E1.

Table 28: Unit costs of evaluated drugs (BNF57 June 09)

Product	£/mg
Folinic Acid non-proprietary	0.3006
Oxaliplatin non proprietary	3.1350
5FU non proprietary	0.0128
Capecitabine	0.0049
Irinotecan	1.3023

Drug utilisation

For the first-line line comparison the duration of treatment, average dose and subsequent total cost of each of the oxaliplatin containing regimens was based upon that observed within the NO16966 study. This provides an empirical basis for the assumptions and also is consistent with the observed and modelled health benefits of the interventions. The table below shows the mean per cycle dose in the NO16966 study for each regimen by drug.

Table 29: Mean dose (mg) per cycle observed in NO16966 study by arm (ITT)

Study Arm (ITT)	Capecitabine	5-FU Bolus	5-FU infusion	Leucovorin	Oxaliplatin	Bevacizumab
B-XELOX	43,562				208	548
B-FOLFOX-4		1,327	2,027	686	134	362
XELOX	45,327				214	521
FOLFOX-4		1,342	2,059	700	138	411

The data in the table above was used to calculate the relative dose intensity per cycle (actual dose per cycle / protocol dose per cycle) that was applied in the model. Relative dose intensity per cycle for the irinotecan containing regimens was assumed to be 93% based on a study by Douillard et al 2000.

Table 30: Relative dose intensity per cycle used in the model

	B-XELOX	B-FOLFOX	XELOX	FOLFOX / FOLFIRI
Bevacizumab	N/A	N/A	0%	0%
Oxaliplatin	88%	87%	91%	89%
Folinic	0%	94%	0%	96%
5-FU	0%	92%	0%	93%
Capecitabine	86%	0%	89%	0%
Irinotecan	0%	0%	0%	93%

Drug administration, pharmacy, and monitoring costs per cycle

A table summarising the resource use by regimen is presented in Appendix E1.

Drug administration costs

Table 31 below lists the administration costs used in the model. These costs were taken from the NHS reference costs 2007/8. Other treatment costs (i.e. chemotherapy drugs including any pharmacy dispensing on-costs and associated drugs to deal with the symptoms or side effects of the chemotherapy drugs themselves) are excluded from NHS reference costs associated with the delivery of chemotherapy and thus were included separately. Monitoring is also not included in the chemotherapy delivery costs listed in the 2007/8 references costs and thus was also costed separately.

Administration of FOLFOX and FOLFIRI involves either two consecutive 22 hour infusions or one 48 hour infusion, these can be delivered either through an ambulatory pump where the patient spends the nights after day 1 at home or though a hospital-based pump where the patient is required to spend two nights in the hospital. Therefore two separate reference costs were required in order to account for these two separate methods of administration. The proportions of patients requiring each respective method of administration was estimated via clinical expert opinion (appendix E2). It was estimated that the vast majority 95% of patients will receive 5-FU infusions via an ambulatory pump and only 5% via as an inpatient in the hospital. Variations in this assumption were evaluated within the one way sensitivity analysis.

For patients staying overnight, the elective inpatient reference cost from HRG PA44Z: “Elective inpatient stay for Neoplasm diagnoses” was used; those using the ambulatory pump where costed using the day case cost for delivery of complex chemotherapy (HRG SB14Z).

Table 31: Drug Administration Daycase Costs (inflated to 2009 costs) per cycle

Regimen	Reference cost HRG code / reference	Day 1 of cycle	Day 2 of cycle	Chemotherapy delivery cost per cycle
FOLFOX-4 / FOLFIRI dG (using ambulatory pump for 5-FU)	SB14Z: Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	£317.28	£227.10	£544.38
	SB15Z: Deliver subsequent elements of a chemotherapy cycle			
FOLFOX / FOLFIRI without ambulatory pump – overnight inpatient stay	PA44Z: Elective inpatient stay for Neoplasm diagnoses (average length of stay 1.44 days)	£1,052		£1,052
B-XELOX / XELOX B-FOLFOX-6 / FOLFOX-6 FOLFIRI mdG (using ambulatory pump for 5-FU)	SB14Z: Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance.	£317.28	-	£317.28

Pharmacy costing

Pharmacy costs are <u>not</u> included within the drug delivery reference costs and therefore were costed separately. These costs were estimated using the same classification employed by the SCHARR evaluation of bevacizumab (Tappenden P et al, 2007). Each infusion preparation was classed as being a “complex” pharmacy preparation and each bolus preparation or oral medication classed as a “simple” pharmacy preparation. Unit cost for complex and simple preparations were taken from the SCHARR analysis and uplifted from 2005 to 2009 costs using the healthcare inflation index published within the PSSRU report 2008.

Table 32: Pharmacy Unit costs

Pharmacy preparation type	2005 SCHARR	Inflated 2009
Complex	£38	£42
Simple	£23	£25

Administration of APAS

It is expected that it will take approximately 5 minutes each cycle for the pharmacist to update the registry system required for the APAS. This equates to £4 per cycle based on the cost of one hour of a hospital pharmacist's time taken from the PSSRU report 2008.

Ambulatory Pump costing

It was assumed that disposable 48hr elastomeric 'balloon' pumps are used and that the delivery of 5FU is interrupted after 22 hours (de Gramont based regimens only), rather than the use of two 24hr pumps, which would be more costly for delivering the FOLFOX-4 regimen.

The cost of the pump was estimated to be £35, based on a 48hr pump provided by a large medical supplier (Baxter UK website, Folfusor SV2 (product code: 2C4702K) http://www.ecomm.baxter.com/ecatalog/browseCatalog.do?lid=10011&hid=10000&cid=10001&key=bf61f5fe7228a1d177d07ee7eb8398a&pid=442402).This cost was assumed to be part of the pharmacy on-costs and therefore in addition to the HRG reference costs used to calculate the cost of a hospital visit for drug administration.

Regular district nurse visits

CVAD's are flushed at the end of each 5FU administration equivalent to one per cycle (Expert opinion). The line flush was assumed to be included within the routine drug administration cost for patients staying in the hospital overnight. However for patients using an ambulatory pump a one hour district nurse visit per cycle to flush the line was accounted for in the analysis.

Homecare

It is expected that when delivered in the home by a homecare service provider the cost of delivering the regimens will differ slightly from the hospital setting. However there is currently negligible use of homecare for the treatment of mCRC patients (Expert Opinion). Hence the effect of using a homecare provider was not considered relevant to the decision problem and is therefore not included in the analysis.

Treatment cycles per patient

Mean number of cycles per month

As illustrated by the table below, the cycle duration observed in the NO16966 was longer than that stipulated in the protocol.

Table 33: Mean number of cycles per month observed in NO16966

	FOLFOX	FOLFOX+P	FOLFOX+B	XELOX	XELOX+P	XELOX+B
Per Protocol (days)	14.00	14.00	14.00	21.00	21.00	21.00
Actual Cycle duration (days)	16.7	16.8	16.2	23.1	23.5	23.0
	5-FU-based regimens			**Capecitabine-based regimens**		
Average cycle duration (days)	16.55			23.21		
Cycles per month used in model	**1.84**			**1.31**		

The average number cycles per month across the 5-FU based arms in the NO16966 was used to calculate monthly treatment costs for each of the 5-FU based regimens in the economic analysis. Likewise the number of cycles per month for the capecitabine based regimens in the economic analysis was derived from the average number cycles per month of all the XELOX based arms in the NO16966 study.

Mean treatment duration per patient in the NO16966

Kaplan-Meier survival analysis was used to calculate the mean treatment duration based on the time from first dose to the time until cessation of treatment as recorded in the NO16966. The Kaplan-Meier curves (shown below) were considered sufficiently complete not to require any extrapolation of the curves.

It was assumed that the time on treatment is correlated to the duration of PFS. Therefore rather than using the Kaplan-Meier curves directly in the model the proportion of patients on treatment out of those still in PFS was applied to the extrapolated PFS curves used in the model.

It was assumed that the relative treatment duration (treatment duration / PFS) is the same for irinotecan containing regimens as was observed for the FOLFOX regimen in the NO16966.

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Figure 20: Kaplan-Meier plot of time to treatment cessation in the NO16966 by regimen

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Supportive care, monitoring, adverse events and CVAD costs

Monthly progression free survival monitoring costs

Consultations with an oncologist were assumed to take place approximately every month (Expert Opinion) The cost of each visit applied in the model was £125.14 (2007/8 reference costs: 370; Consultant Led: Follow Up Attendance Non-Admitted Face to Face inflated to 2009 costs).

Based on expert opinion patients were assumed to receive a CT scan every 3 months irrespective of the regimen they were receiving and bloods were assumed to be taken every cycle. The unit costs of taking bloods and performing each CT scan, £3 and £135 respectively (Renal Cell Carcinoma MTA, 2009).

Adverse Events

The costs of the treatment related adverse events, as observed in the NO16966 study were incorporated into the economic model.

Adverse events (AEs) included within the economic model for costing purposes had to meet the following selection criteria:

- Grade 3 or 4 AEs (no grade 5 events in study NO16966)
- An incidence equal to or greater than 2% was observed in any of the arms of the trial.

The expected cost per episode of each individual adverse event was calculated as follows: Number of event * / the number treated * the estimated cost of treating the event.

The sum of the expected cost for each adverse event then generated the total expected cost of adverse events for each arm in the model. This total cost of adverse events is included within the model as a lump sum in the first model cycle. The subsequent total expected average cost of treating grade 3 and 4 adverse events for each intervention are presented in the results section.

Table 34: Unit cost for treatment of adverse events

Adverse event	Unit cost (£'s)	Reference / comment
cardiac disorders	1,201	Ref costs 2006/7
Diarrhoea	237	LRIG 2006 Erlotinib
Febrile Neutropenia	1,575	Ref costs 2006/7
hypertension	200	Palmer 2004
infections (excl. Febrile neutropenia)	1,077	Ref costs 2006/7
Neurotoxicity	18	LRIG 2006 Erlotinib
Neutropenia / granulocytopenia	140	LRIG 2006 Erlotinib
Palmar-plantar erythrodysaesthesia syndrome (Hand and Foot)	137	York CRD 2004, September 2004
Stomatitis	819	Capri et al 2003
venous thromboembolism	741	Ref costs 2006/7
Vomiting / Nausea	240	Ref costs 2006/7

Published NHS reference costs were used were available, otherwise adverse event costs were sourced from the literature. The safety population (patients having received at least one administration of study drug) from the NO16966 study was utilised for the purposes of adverse event data. Treatment costs taken from the reference costs were a weighted average of the most applicable HRG's (see Appendix E1 for HRG's included)

The frequency and type of adverse events included in the model, according to the selection criteria above, are summarised in the following table:

Table 35: Incidence (%) of adverse events costed in the model from NO16966

Adverse event	FOLFOX	XELOX	B-FOLFOX	B-XELOX
cardiac disorders	1.39	0.92	5.67	6.73
Central line infection	3.09	0.31	21.81	7.31
Diarrhoea	11.42	20.31	3.97	9.36
Febrile Neutropenia	4.78	0.92	6.23	4.39
hypertension	0.77	0.76	10.76	40.35
infections (excl. Febrile neutropenia)	7.10	6.56	1.13	12.87
Neurotoxicity	16.51	17.10	11.90	3.51
Neutropenia / granulocytopenia	43.52	7.02	1.98	7.31
Palmar-plantar erythrodysaesthesia syndrome (Hand and Foot)	1.23	6.11	7.08	1.46
Stomatitis	2.01	1.22	4.53	3.51
venous thromboembolism	6.33	3.82	18.13	17.84
Vomiting / Nausea	7.25	7.94	0.28	1.75

Central Venous Access Device (CVAD) costing

Insertion of a CVAD was assumed to require a separate hospital visit, consistent with current clinical practice. The cost of a CVAD insertion was taken from reference costs 2007/8 HRG QZ14A (Day Case): "Vascular Access except for Renal Replacement Therapy with CC".

A count of CVAD's installed, removed and replaced was captured during the NO16966 study. Considering the multi-national design of the NO16966 trial and large geographical variation in CVAD clinical practice, we consulted with clinical experts on the typical usage of CVAD's in the England and Wales for the two interventions in question. CVAD usage was considered routine practice for 5-FU, but very rare for the capecitabine containing regimens. It was estimated that a CVAD was placed in 100% and 10% of patients receiving the 5-FU-based and capecitabine-based regimens respectively. The effect on the ICER of changes to this assumption was evaluated within the one-way sensitivity analysis.

Occasionally in clinical practice CVAD's need to be replaced; the percentage of patient with a CVAD that required it to be replaced was captured within the NO16966 study. This proportion was assumed not to be affected by geographical location and therefore added to the number patients required a CVAD to estimate the mean number of CVAD placements required for each therapy.

Cost for removal of the CVAD was estimated to be minimal and therefore excluded as the CVAD is often left installed after treatment and if removal is required, it was assumed this would happen during the last chemotherapy administration.

Unit costs used in the calculation of CVAD line placements and maintenance are show in the table below.

Table 36: CVAD Unit Costs

Event	Assumption	Cost	Reference
CVAD insertion or replacement	Procedure performed prior to Day 1 of cycle as an outpatient visit	£502	2007/8 HRG QZ14A (Day Case): "Vascular Access except for Renal Replacement Therapy with CC"
CVAD line flush	One line flush per cycle.	£37.22	Ref costs 2007/8 CN301AF: District Nursing Services : Adult : Face To Face
CVAD removal	No associated NHS costs	£0	n/a

Progressive Disease health state cost

As displayed in Appendix E5, post protocol treatments in the NO16966 study were similar across all of the arms of the study both in terms of the total proportion of patients receiving post protocol treatments and also the mix of drugs used. It was therefore assumed that there was no difference in treatment cost between the interventions post progression on first-line. Instead monthly supportive care costs of £600 sourced from a previous economic evaluation of bevacizumab in mCRC (Tappenden et al 2007) were applied to each intervention in the Progression health state.

7.2.9.2 How were the resources measured?

See section above

7.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

See section above

7.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

As displayed in Appendix E4 post protocol treatments in the NO16966 study were similar across all of the arms of the study both in terms of the total proportion of patients receiving post protocol treatments and also the mix of drugs used. It was therefore assumed that there was no difference in treatment cost between the interventions post progression on first-line. However monthly supportive care costs of £600 sourced from a previous economic evaluation of bevacizumab in mCRC (Tappenden et al 2007) were applied in the Progression health state.

7.2.9.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The majority of the costs were sourced from the recently published reference costs 2007/8.

Pharmacy costs and post progression monthly costs were sourced from the previous bevacizumab technology appraisal publish in the paper by Tappenden et al, 2007.

See section 7.2.9.1 for more detailed information on estimation of cost.

7.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

Unit costs are provided in section 7.2.9.1 above.

All drug acquisition costs were based on the published list price (BNF57) accept for bevacizumab which is charged at a fixed price per treatment cycle of £1200 and £800 for XELOX and FOLFOX based regimen respectively. Oxaliplatin is provided free of charge for patients enrolled in APAS.

7.2.9.7 Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure would be required for the administration of bevacizumab

7.2.9.8 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Only costs relating to resources under control of the NHS and PSS were included. Prices were taken from National reference costs 2007/2008, BNF 57, and PSSRU 2008. Only when costs could not be identified from these sources were alternative sources, such as literature review or expert opinion, utilised to inform the model.

7.2.9.9 Were resource values indexed to the current price year?

Costs were inflated to 2009 costs based on the PSSRU 2008 cost index

7.2.9.10 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

It is assumed there is minimal incremental cost for providing bevacizumab in hospital. Patients attend the hospital on day 1 of the treatment cycle for when receiving either XELOX and FOLFOX to receive a 2 hour infusion of oxaliplatin followed by either collecting oral capecitabine or being connected to an ambulatory pump for the 5-FU infusion. Bevacizumab is infused immediately after oxaliplatin in typically 30 minutes. It is understood that the majority of the healthcare professionals' time is spent in the preparation and set up or the set of infusions, which would apply irrespective of whether the patient was receiving XELOX / FOLFOX alone or in combination with bevacizumab. Any additional cost associated with the bevacizumab infusion was assumed to be covered by the additional £42 per cycle included under pharmacy costs.

The monthly resource costs of patients in the progressive health state were assumed equal regardless of whether the patient received bevacizumab or not due to the relatively equal balance observed in the 2nd-line treatments utilised in the NO16966 trial (see Appendix E4).

Further details of the methods used for estimating resource use are described in section 7.2.9.1

7.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Both costs and health benefits were discounted monthly at a rate equivalent to 3.5% annual discount rate.

7.2.11 Sensitivity analysis

7.2.11.1 Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis is preferred for translating the imprecision in all input

variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

7.2.11.2 For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.2.11.3 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

Selection of the correct parametric function to inform the survival analysis may be considered a source of structural uncertainty and therefore alternative functions were evaluated. Scenarios were thus explored whereby the Weibull curves were used to estimate PFS and OS survival curves for the entire curve not only the extrapolated section of the curve. The results are reported along with the results of the one-way sensitivity analysis.

7.2.11.4 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

Below is a list of all variables subject to one-way sensitivity analysis:

- Utility Values
  - 1st line treatment health state (PFS_T)
  - PFS post treatment health state (PFS_{PT})
  - Progression health state (PD)
- Survival Analysis
  - Time horizon set to 5 years as opposed to the default of 8 years
  - Weibull used for PFS
  - Weibull used for OS
  - No treatment effect after the time-point of median follow-up
- Clinical Practice Assumptions
  - Proportion of patients requiring hospital transport
  - Proportion of FOLFOX patients using ambulatory pumps
  - Proportion of patients requiring CVAD insertion
- Unit Costs
  - CVAD insertion cost
  - Day 1 administration cost

- Day 2 administration cost
- Pharmacy cost (complex infusion)
- Pharmacy cost (simple infusion)
- Cost of Progressive Disease Health State
- Total B Cape Ox Adverse Event costs
- Total FOLFOX Adverse Event costs

7.2.11.5 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

PSA was undertaken. The sample size was set at 500 and then the PSA was re-run at a sample size of 1,000; no meaningful difference was seen between the two results. Distributions were applied around the following parameters to reflect parameter uncertainty in the model:

- Utilities values
- Unit costs
- Monthly supportive care costs
- Adverse event probabilities
- Survival curves parametric parameters
- PFS and OS monthly Kaplan-Meier estimates
- Proportion of patients receiving treatment out of those remaining in PFS for each month

A list of all parameters included in the PSA along with assumed distributions and the value of priors is provided in Appendix E3

7.2.12 Statistical analysis

7.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

Transition probabilities were not calculated as the model was based on an area under the curve design. The derivation of the survival curves is described in section 7.2.6.8.

7.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities implicit in the PFS and OS curves used in this area under the curve do vary over time.

7.2.13 Validity

7.2.13.1 Describe the measures that have been undertaken in order to validate and check the model.

The internal validation and debugging of the model was performed by an external company specialized in the development and validation of decision analytic models used for health economic analyses and who had not been involved in the development of the model. The following validation procedures were performed:

- Check of completeness of reported results (health outcomes, economic outcomes) as compared to other published economic evaluations targeting the same indication; Tappenden et al, Cetuximab for 1st line treatment of mCRC.

- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, adverse event costs, cost of study drugs and administration, discount rates, and health utilities.

- The methods of extrapolation (exponential and Weibull) were replicated and verified. Cost and utility inputs were validated with the evidence submission report.

To externally validate the model the estimated PFS and OS for the bevacizumab containing regimens estimated by the model were compared with real life data from the BRiTE and BEAT observational data and also considered in light of the median results of the NO16966 study.

7.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

7.3.1 Base-case analysis

7.3.1.1 What were the results of the base-case analysis?

First-line analysis

The results of the base-case analysis are provided below. The mean results of the probabilistic sensitivity analysis (PSA) (see section 7.3.3) were virtually identical to the deterministic results; hence all the figures presented in this section (7.3.1.1) represent the deterministic results. The PSA means are provided along side the scatter plots in the sensitivity analysis (section 7.3.3)

Costs

The figure below shows the total cost per patient for each of the interventions / comparators by category of cost.

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Figure 21: Mean total costs per patient

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It can be seen that drug acquisition and administration costs are the main drivers of cost variance between the regimens.

XELOX resulted in the lowest total cost of all the regimens with a total cost per patient of [redacted]. B-XELOX cost [redacted] representing the least expensive of the bevacizumab regimens.

B-XELOX was similar in terms of total cost per patient to the comparator regimen most used in the UK: FOLFOX.

The data displayed above in figure 21 is represented in tabular format in tables 37 and 38 below.

Table 37: Total cost for each intervention per patient

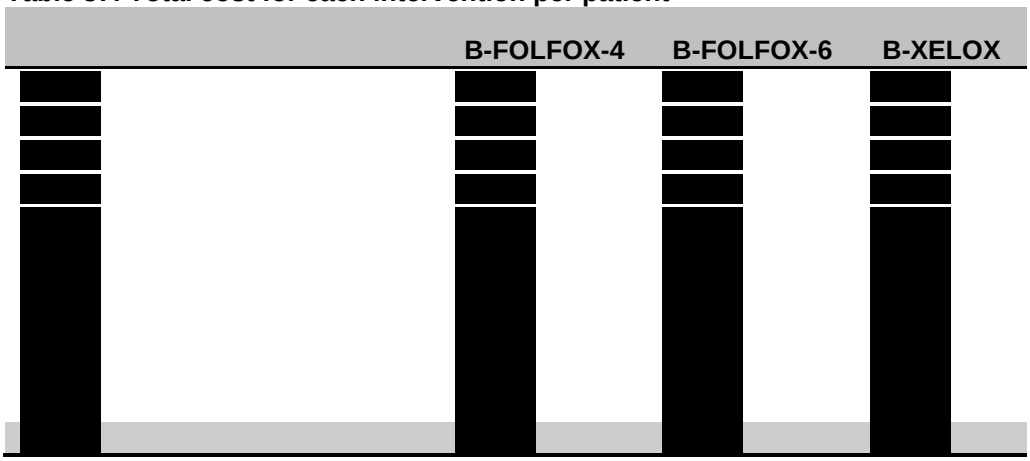
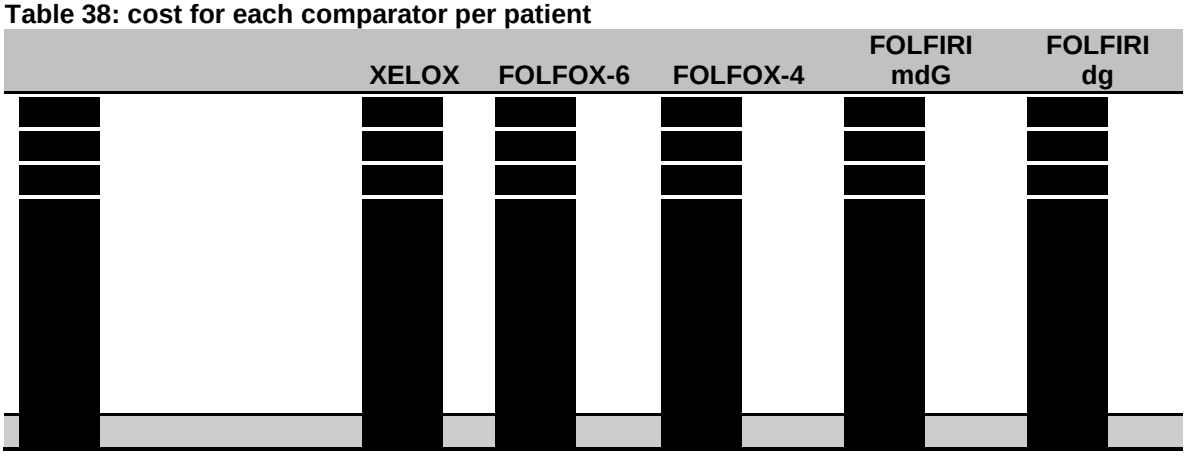


Table 38: cost for each comparator per patient



Mean time in each health state and Quality-Adjusted Life Years

Table 39 shows that the combination of bevacizumab in combination with oxaliplatin and either 5-FU / capecitabine results in a mean gain of 2.9 months of life compared with 5-FU/capecitabine in combination with oxaliplatin alone. Compared with FOLFIRI, the bevacizumab combination therapy resulted in an increase of 4.0 months of life.

Just over two thirds of the extension in life resulted from an extension of PFS. The remaining benefit therefore resulting from increased time in post progression survival. This is consistent with the median results from the study, which showed 30% of the increase in OS coming from the PD health state. The duration of PFS and OS for the

bevacizumab arms are consistent with that observed in the BRiTE registry data, which reported median PFS in oxaliplatin-based regimens of 11.4 months (Kozloff 2007) and OS of 25.1 months for all patients (Grothey et al; OS split by combination chemotherapy not reported) and the BEAT study which reported median PFS and OS of 11.6 and 24.7 months respectively in the bevacizumab in combination with oxaliplatin-based chemotherapy arms.

Table 39: Time (months) spent in each health state till death per patient (undiscounted)

	B-XELOX	B-FOLFOX	XELOX	FOLFOX	FOLFIRI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

When the mean extension in each health state was weighted to account for quality of life it was seen that bevacizumab in combination with oxaliplatin and either 5-FU / capecitabine results in an increased QALY per patient of [redacted] over XELOX/FOLFOX and FOLFIRI respectively. The incremental QALY is mainly related to a longer stay in the PFS health state for the patients given bevacizumab than that observed for patients receiving the comparator regimens.

Table 40: QALYs per patient

	B-XELOX	B-FOLFOX	XELOX	FOLFOX	FOLFIRI
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 41: Incremental QALYs per patient

	XELOX	FOLFOX	FOLFIRI
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Incremental cost effectiveness results

The mean incremental cost and QALY for each therapy option is displayed on the cost-effectiveness plane below. XELOX dominates all the other comparators that do

not contain bevacizumab as it is more or equally effective whilst being less expensive than these other comparators. B-XELOX dominates all of the bevacizumab containing regimens. Hence B-XELOX and XELOX represent the efficiency frontier as illustrated in figure 22 below.

Figure 22: Simultaneous incremental results

Table 42: Mean Incremental cost per patient

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
B-FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 43: Mean ICERs (£/QALY) per patient

	COMPARATOR				
Intervention	**XELOX**	**FOLFOX-6**	**FOLFOX-4**	**FOLFIRI mdG**	**FOLFIRI dg**
B-XELOX	£34,170	£594	Dominant	£9,192	Dominant
B-FOLFOX-6	£75,211	£41,388	£22,958	£38,835	£22,292
B-FOLFOX-4	£102,434	£68,154	£50,307	£58,575	£42,031

The incremental cost effectiveness ratios (£/QALY) for each of the interventions compared to each of the comparators is provided in table 43 above. Highlighted in the table are the ICER's that are of most relevance to the decision problem.

Comparing the two regimens on the efficiency frontier (see figure 22 above) B-XELOX and XELOX results in an incremental cost per QALY of £34,170.

A small number of patients may not be suitable for capecitabine making the incremental cost effectiveness of adding bevacizumab to the oxaliplatin containing therapy they currently receive also of relevance. When adding bevacizumab to FOLFOX-6 the ICER is £41,388.

Where B-XELOX replaces the most used regimen FOLFOX-6 there is minimal cost impact due to the administration savings associated with moving from the 2 weekly FOLFOX-6 regimen to the 3 weekly B-XELOX regimen, which offset much of the incremental cost associated with providing bevacizumab (APAS) resulting in an ICER of £594.

B-XELOX and B-FOLFOX-6 may also be considered cost effective when replacing FOLFIRI, for patients that are suitable for oxaliplatin-based regimens, with a cost per QALY gained of £9,192 for B-XELOX vs FOLFIRI mdG and £38,835 for B-FOLFOX-6 vs FOLFIRI mdG.

Second-line analysis

The table below shows the results of the cost-effectiveness analysis performed for combining bevacizumab with FOLFOX-4 in the 2nd line setting.

Table 44: Cost effectiveness of B-FOLFOX-4 vs FOLFOX based on E3200

	B-FOLFOX-4	FOLFOX-4	Incremental	Incremental LY	Increment QALY
[redacted]					
ICER (£/QALY)					**£102,644**

Notes:
Mean PFS and OS taken from Shiroiwa et al 2007 (Weibull regression of reported E3200 survival curves)
Discounting not performed but not expected to impact results

The APAS has been applied (12 month cap assume not to impact results)

As can be seen from the above that in the second-line setting the ICER when comparing B-FOLFOX-4 to FOLFOX-4 is outside the range that is usually considered cost effective in the UK according to NICE's criteria. If the assumption is made that B-XELOX and B-FOLFOX-4 have equivalent efficacy in the second-line setting (as demonstrated in the first-line setting) one would expect the ICER for B-XELOX vs XELOX to reduce to approximately £90,000 per QALY. The far higher ICER's in the second-line setting to those of the first-line are most likely driven to a large extent by the higher dose which was used in the E3200 study relative to that used in the NO16966 study.

7.3.2 Subgroup analysis

7.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

As per the final scope no sub-group analysis was performed.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

B-XELOX vs XELOX

One way sensitivity analysis

The effect of changes in parameter values for the comparison B-XELOX with each comparator is shown below.

Table 45: One-way sensitivity analysis of B-XELOX vs XELOX to changes to mean parameter estimates (base case £34,170)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS_T Utility value	0.77	0.73	0.81	£34,452	£33,892
PFS_{PT} Utility value	0.79	0.75	0.84	£35,199	£32,965
Progression Utility Value	0.68	0.64	0.72	£34,710	£33,646
Survival Analysis					
Weibull OS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£34,170	£36,857
Weibull PFS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£34,170	£32,592
assume treatment effect post follow-up 0 = yes 1 = no	0	0	1	£34,170	£40,202
Time horizon (years)	8	5	10	£37,936	£34,049
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£34,141	£34,189
% pts with CVAD insertion 0 = UK expert opinion, 1=recorded in trial	0	0	1	£34,170	£34,406
Unit Costs					
Cost of CVAD installation	£502	£301	£703	£34,169	£34,171
Cost of hospital funded transport per visit	£29	£18	£41	£34,158	£34,181
Cost per consultation with oncologist	£125	£75	£175	£33,827	£34,513
Cost of a CT scan	£135	£81	£189	£33,968	£34,372
Cost of administration day 1 of cycle	£317	£190	£444	£33,760	£34,579
Pharmacy cost (complex infusion)	£42	£25	£59	£33,256	£35,084
Pharmacy cost (simple infusion)	£25	£15	£35	£34,137	£34,203
Cost of Progressive Disease Health State	£600	£360	£840	£33,046	£35,294
Total B Cape Ox Adverse Event costs	£248	£149	£347	£34,766	£33,574
Total FOLFOX Adverse Event costs	£334	£200	£467	£33,368	£34,972

Figure 23: Tornado diagram for B-XELOX vs XELOX

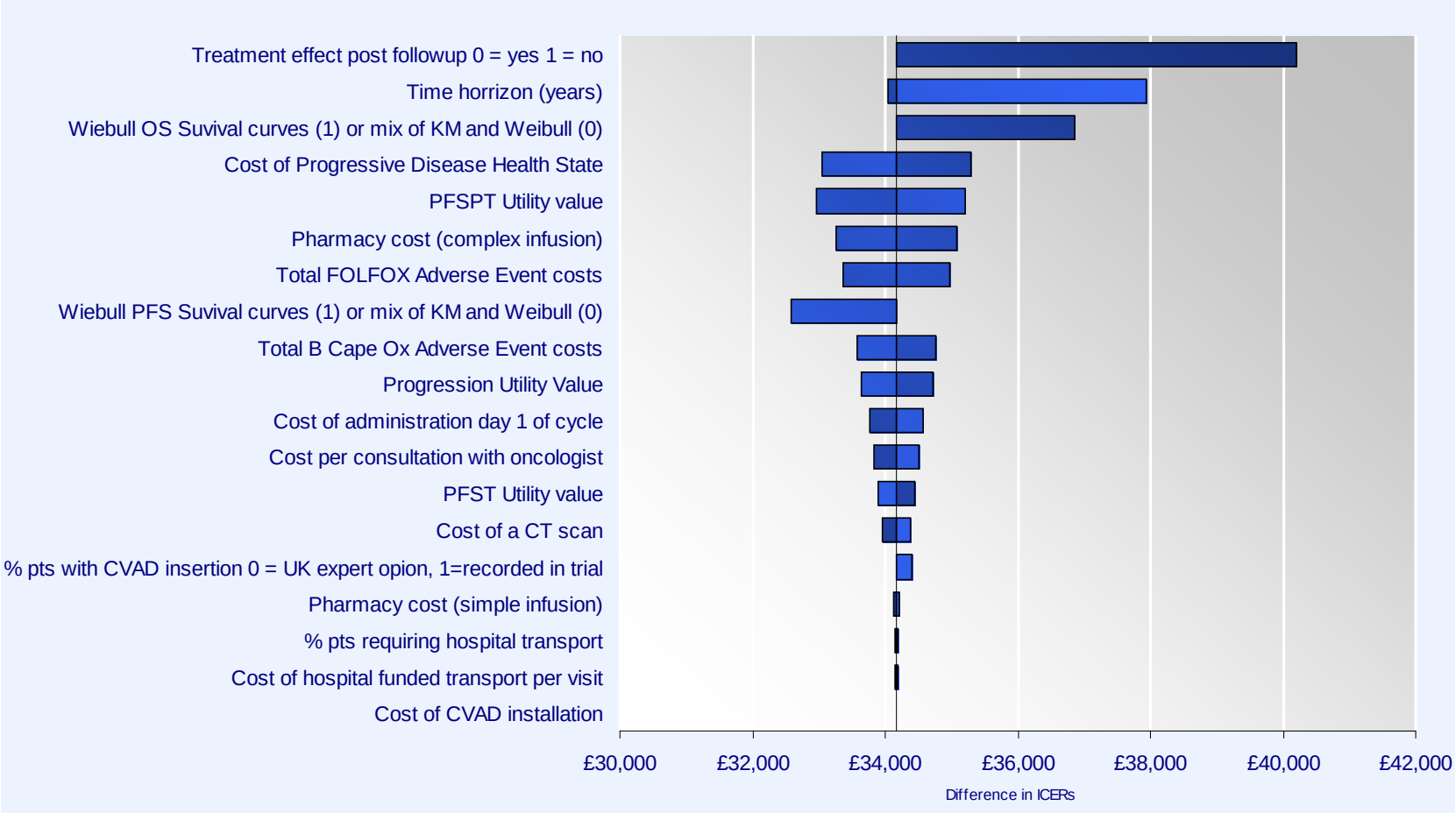
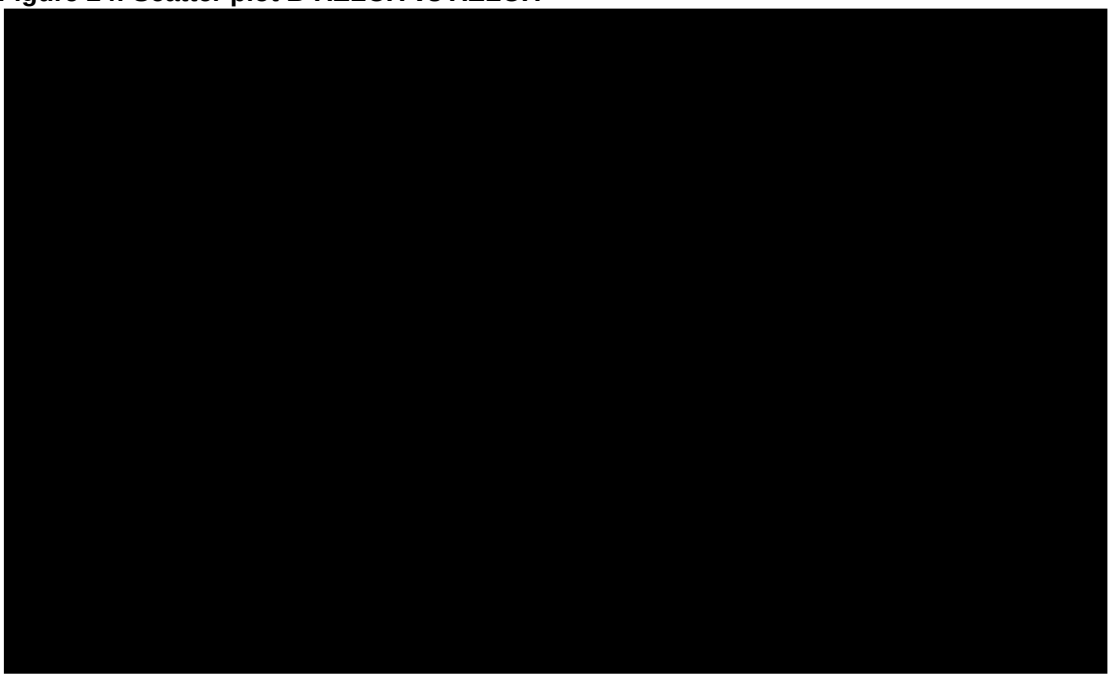
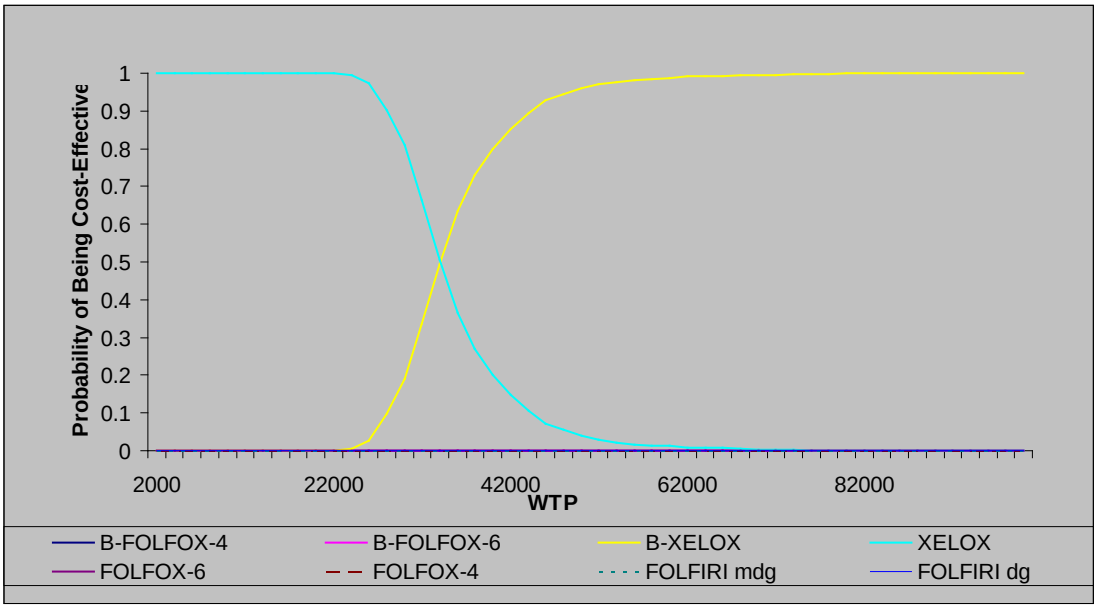


Figure 24: Scatter plot B-XELOX vs XELOX



Mean ICER = 34,011

Figure 25: Cost Effectiveness Acceptability Curve



B-FOLFOX-6 vs FOLFOX-6

Table 46: One-way sensitivity analysis of B-FOLFOX-6 vs FOLFOX-6 to changes to mean parameter estimates (base case £ 41,388)

Parameter modified	Base value	Low value	High value	ICER Low	ICER High
Utility Values					
PFS_T Utility value	0.77	0.73	0.81	£42,210	£40,597
PFS_{PT} Utility value	0.79	0.75	0.84	£42,154	£40,469
Progression Utility Value	0.68	0.64	0.72	£42,046	£40,750
Survival Analysis					
Weibull OS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£41,388	£44,919
Weibull PFS Survival curves (1) or mix of KM and Weibull (0)	0	0	1	£41,388	£38,915
assume treatment effect post follow-up 0 = yes 1 = no	0	0	1	£41,388	£49,324
Time horizon (years)	8	5	10	£46,275	£41,231
Clinical Practice Assumptions					
% pts requiring hospital transport	30%	0%	50%	£41,293	£41,451
% FOLFOX pts with ambulatory pump	95%	50%	100%	£41,388	£41,388
% pts with CVAD insertion 0 = UK expert opinion, 1=recorded in trial	0	0	1	£41,388	£40,961
Unit Costs					
Cost of CVAD installation	£502	£301	£703	£41,329	£41,447
Cost of hospital funded transport per visit	£29	£18	£41	£41,350	£41,426
Cost of 5-FU pump	£35	£21	£49	£41,237	£41,538
Cost per consultation with oncologist	£125	£75	£175	£40,959	£41,817
Cost of a CT scan	£135	£81	£189	£41,185	£41,591
Cost of district nurse visit	£37	£22	£52	£41,228	£41,548
Cost of administration day 1 of cycle	£317	£190	£444	£40,024	£42,752
Cost of administration day 2 of cycle	£227	£136	£318	£41,388	£41,388
Cost of inpatient stay of administration	£1,052	£631	£1,473	£41,388	£41,388
Pharmacy cost (complex infusion)	£42	£25	£59	£39,518	£43,258
Pharmacy cost (simple infusion)	£25	£15	£35	£41,279	£41,497
Cost of Progressive Disease Health State	£600	£360	£840	£40,349	£42,426
Total B Cape Ox Adverse Event costs	£407	£244	£569	£42,371	£40,404

Figure 26: Tornado diagram for B-FOLFOX-6 vs FOLFOX-6

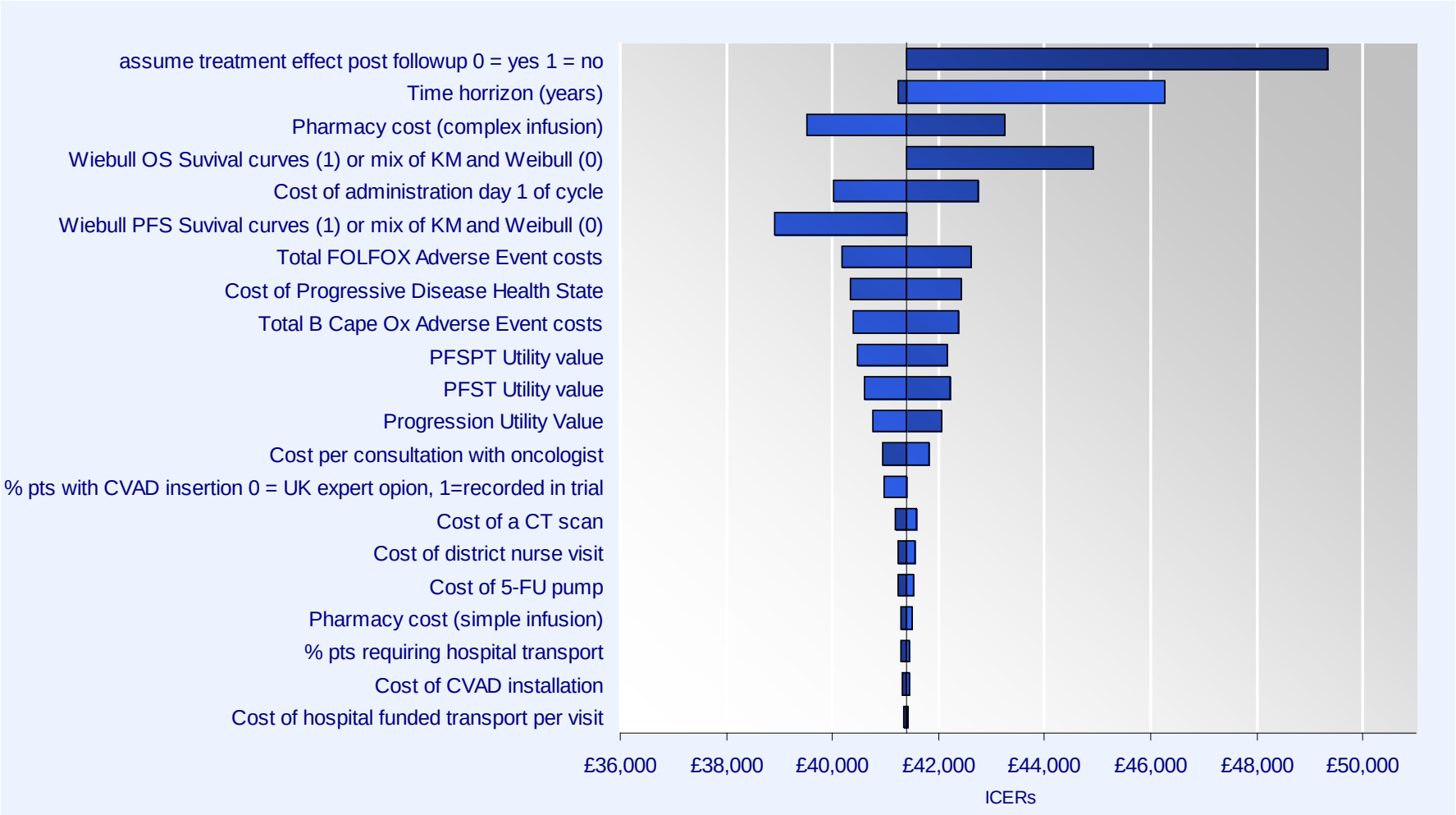


Figure 27: Scatter plot B-FOLFOX-6 vs FOLFOX-6

Mean ICER = £41,518

7.3.3.2 What are the key drivers of the cost effectiveness results?

The results of the sensitivity analysis suggest that the results are not influenced greatly by changes to clinical practice assumptions, resource unit costs or changes to utility values. This is not that surprising as these changes are applied to both arms of the model.

The results are most sensitive to changes in the assumed treatment effect post the point of median follow-up.

7.3.4 Interpretation of economic evidence

7.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The results comparing B-XELOX vs FOLFOX-4 without APAS are consistent with study by Lewis et al, which reported an ICER of £25,806 compared to an ICER of [redacted] in this analysis. The second line results without the APAS [redacted] per LYG) are not too dissimilar to those reported by Shiroiwa et al who estimated a cost of life year gained of 14.1mYen or £70,000 (based on exchange rate used in Shiroiwa paper).

7.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

The base case of the economic evaluation is relevant to all patients in first or second line mCRC who would be considered suitable for oxaliplatin-based combination chemotherapy. The economic evaluation is therefore of particular relevance to patients that would currently receive oxaliplatin based regimens.

7.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths

a) The incremental clinical effects of B-XELOX and B-FOLFOX-4 compared to XELOX and FOLFOX-4 are based upon a large randomised head to head phase III study, which demonstrated a significant treatment effect of adding bevacizumab to standard chemotherapy. Consequently the certainty of the treatment effect of bevacizumab and the subsequent incremental clinical advantages of adding bevacizumab to either XELOX or FOLFOX-4 is strong.

b) Very little extrapolation of the primary endpoint, PFS, was required due to the maturity of follow-up in the NO16966 RCT.

c) A very mature and detailed dataset was available for first-line treatments in the NO16966 study therefore the mean dose, treatment frequency, and

duration of treatment could be estimated with a high level of certainty for the oxaliplatin comparisons.

Weaknesses

a) No head-to-head data is available for comparison for B-XELOX or B-FOLFOX with FOLFIRI. Whilst the mixed treatment comparison is comprehensive it did not differentiate between the IFL regimen that was typically used in the United States and the FOLFIRI regimen currently used in both the US and UK. Therefore there is a lack of certainty around the relative effectiveness of FOLFIRI compared to the other comparisons.

b) The utilities used in the 1st line health state are based on EQ-5D data collected in the UK for the relevant population however this was based on treatment with FOLFIRI in combination with cetuximab and not oxaliplatin or bevacizumab containing regimens. However changes to the utility values did not greatly impact the ICERs (see sensitivity analysis)

c) Utility values for patients in the PFS_{PT} health state were based partly on expert opinion. However the sensitivity analysis demonstrated that this is not a major driver of the results.

d) The aggregated nature of the progressed health state may appear an over-simplification of the natural disease progression of mCRC patients.

7.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

A more detail analysis could be performed for using bevacizumab in the 2nd line setting however this was not performed given the relatively high ICER currently reported for 2nd line.

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The results of the economic analysis suggests B-XELOX dominates B-FOLFOX and thus the budget impact calculations are based on a positive recommendation for B-XELOX is recommended for 1st line mCRC for all patient suitable for this regimen and B-FOLFOX-6 is recommended in patients unsuitable for capecitabine.

Table 47: Estimated annual budget impact of recommending B-XELOX and secondly B-FOLFOX for patient not suitable for capecitabine

		Incremental Cost			Year				
		Weighted Avg	B-FOLFOX-6	B-XELOX	2010 £000's	2011 £000's	2012 £000's	2013 £000's	2014 £000's
FOLFOX-6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLFOX-4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
XELOX	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLFIRI mdG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FOLFIRI dg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOTAL	Drug Acquisition				**7,586**	**11,379**	**14,927**	**14,927**	**14,927**
	Other Costs				**-1,578**	**-2,366**	**-3,044**	**-3,044**	**-3,044**
	Total				**6,008**	**9,013**	**11,883**	**11,883**	**11,883**

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The eligible population was based on the estimated number of patient currently receiving one of the comparator regimens in England and Wales.

Table 48: Patients Eligible for treatment with B-FOLFOX or B-XELOX

	Incidence England and Wales	% of Incidence of CRC in England and Wales	Reference
Colorectal Cancer	31,119	100%	ONS 2008
Incurable Advance Colorectal Cancer	16,181	52%	Tappenden et al 2007
1st line Chemotherapy	12,979	42%	
excl Clinical Trials	11,421	37%	Synovate Market research, 2009
excl private patients	9,936	32%	Wave 1; Synovate, June 2008
Receive FOLFOX	2,782	9%	
Receive XELOX	2,385	8%	
Receive FOLFIRI	1,192	4%	Synovate Market research, 2009
Eligible Population in NHS	**6,359**	**20%**	

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that the uptake of the bevacizumab would be rapid in the first two years and stabilising in year 3 at 80% usage in patients that would currently receive FOLFOX or XELOX and 15% of patients currently receiving FOLFIRI.

Based on expert opinion it was assumed that 5% of patients currently receiving 5-FU combination therapy would not be suitable for capacitate combination therapy and therefore 5% of the total uptake in patients receiving either FOLFOX or FOLFIRI would be to B-FOLFOX-6 and 95% of this uptake would be to B-XELOX.

It was assumed no patients would receive B-FOLFOX-4.

Table 49: Forecasted uptake of bevacizumab by regimen replaced over 5 year period

Intervention	YEAR				
	2010	2011	2012	2013	2014
Percentage uptake by regimen replaced					
FOLFOX	40%	60%	80%	80%	80%
XELOX	40%	60%	80%	80%	80%
FOLFIRI	10%	15%	15%	15%	15%
Uptake (patients) by regimen replaced					
FOLFOX	1,113	1669	2226	2226	2226
XELOX	954	1431	1908	1908	1908
FOLFIRI	119	179	179	179	179

8.4 What assumption(s) were made about market share (where relevant)?

The current mix of treatments used in 1st line mCRC was obtained through market research conducted from 17th April 2009 – 30th April 2009 involving 50 oncologists across England and Wales. (Synovate market research, 2009)

Based on Expert Opinion (see Appendix E2 for list of experts) it was assumed that 95% of FOLFOX / FOLFIRI is delivered using the mdG schedule.

8.5 What unit costs were assumed? How were these calculated?

Incremental costs were taken from the per patient incremental costs calculated in the economic analysis described in section 7 and reported in section 7.3.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Incremental costs were taken from the per patient incremental costs calculated in the economic analysis described in section 7 and reported in section 7.3.

8.7 Were there any estimates of resource savings? If so, what were they?

It is estimated that by moving from a FOLFOX and FOLFIRI regimen to B-XELOX that there will be cost savings in terms of drug administration cost, pharmacy costs and costs associated with the installation and management of central venous access devices.

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No

9 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

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10 Appendices

10.1 Appendix 1

Summary of Product Characteristics or Technical Manual or drafts

10.2 Appendix 2: search strategy for section 5

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Dialog DataStar was used to search Medline (MEYY), Medline in process (MEIP), Embase (EMYY), Embase alerts (EMBA) and Biosis (BIYY - for abstracts presented at The American Society of Haematology [ASH] annual meeting). The Cochrane Library controlled trials database was searched for clinical trials of bevacizumab in mCRC. Please note the same searches were used to extract randomised and non-randomised studies.

10.2.2 The date on which the search was conducted.

Response

10.2.3 The date span of the search.

Response

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Response

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Response

10.2.6 The inclusion and exclusion criteria.

Response

10.2.7 The data abstraction strategy.

Response

10.3 Appendix 3: search strategy for section 6

The following information should be provided.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- Health Economic Evaluation Database
- NHS Economic Evaluation Database (NHS EED).

Dialog DataStar was used to search Medline (MEYY), Medline in process (MEIP), and Embase (EMYY). HEED and NHS EED were searched using their own search facilities.

10.3.2 The date on which the search was conducted.

The searches of Medline and Embase were conducted on the 4th of June 2009

The search of the other databases were conducted on 15th of June 2009

10.3.3 The date span of the search.

Wherever possible databases were searched from 01/01/2000 to the present. The Cochrane library was tested in its entirety.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Search Strategy for EMYY and MEYY

Economic search for NICE MEDLINE and EI

Attached above is the search strategy and results of the search for economic analyses from Medline and Embase

All bar one identified studies were either not economic evaluations, were costs studies based outside the UK (Drucker) or related to the previous NICE appraisal of bevacizumab and thus did not address the decision problem.

The only study that was not excluded for the aforementioned reasons was: Cost−effectiveness analysis of bevacizumab combined with chemotherapy for the treatment of metastatic colorectal cancer in Japan. Clinical therapeutics, {Clin−Ther}, Oct 2007, vol. 29, no. 10, p. 2256−67, ISSN: 0149−2918. Shiroiwa−Takeru, Fukuda−Takashi, Tsutani−Kiichiro. 2007.

This study was included for the purpose of the second-line analysis but not for the first line analysis as the NO16966 study was not included in the analysis. Costs estimates were not considered to be reliably reflective of UK practice however the estimation of the clinical benefits were consider relevant to the second-line analysis.

Search of HEED

Heed was searched using their recommended taxonomy:

Type of article: both unrestricted and then using: methodological or government or public policy or review of approved studies
Type of economic evaluation: analysis or benefit or consequences or effectiveness or minimisation or utility or illness
Drug name: bevacizumab
Keywords: cost or cost effective (ness) or cost(s) or CBA or CUA or CUA/Decisions or CEA or CEA Monitored or CEA Prompted or CEA / CUA or CEA / CA or CEA ? Decision or CMA
Results

Microsoft Word Document

No knew economic evaluations relevant to the decision problem were identified.

Search NHS EED

http://www.crd.york.ac.uk/crdweb/
Searched strategy**:** bevacizumab and colorectal and economic
4 results were found which all of which were studies already identified by the above searches

..Various links that you may already have:

Search Strategy for EMYY and MEYY for Quality of life data

Quality of life search for NICE MEDLINE an

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Roche's internal database was interigated for relevant health economic analyses.

Economic Evaluation Appendices

Appendix E1: Resource use

Unit cost (£'s)		B-XELOX	B-FOLFOX Modified De Gramont	B-FOLFOX De Gramont	B-FOLFOX De Gramont Inpatient	XELOX	M. de Gramont FOLFOX / FOLFIRI	de Gramont FOLFOX / FOLFIRI	De Gramont FOLFOX / FOLFIRI Inpatient
	Cycles per month	1.31	1.84	1.84	1.84	1.31	1.84	1.84	1.84
	Per cycle pharmacy preparation and dispensing								
42	Pharmacy complex	2	4	6	6	1	3	5	5
25	Pharmacy simple	1	1	2	2	1	1	2	2
	Pharmacy cost per cycle (£'s)	**109**	**193**	**302**	**302**	**67**	**151**	**260**	**260**
	Per cycle administration:								
29	patient transport	0.3	0.3	0.6	0.3	0.3	0.3	0.6	0.3
35	Ambulatory pump		1	1			1	1	
125	Monitoring additional to admin visit								
37	District Nurse Visit		1.00	1.00			1.00	1.00	
317	Administration outpatient 1st day of cycle	1	1	1		1	1	1	
227	Administration Outpatient subsequent visits per cycle	0		1		0		1	
1,052	Administration overnight visits				1				1
	Administration cost per cycle (£'s)	**335**	**407**	**652**	**1070**	**335**	**407**	**652**	**1070**
	Total: admin and pharmacy cost / month	**582**	**1103**	**1754**	**2522**	**527**	**1026**	**1677**	**2445**
	Monthly Monitoring during treatment								
125	Consultation OP appointment in PFS	1	1	1	1	1	1	1	1
3	Bloods	1.31	1.84	1.84	1.84	1.31	1.84	1.84	1.84
135	CT scan once per 3 months in PFS	0.33	0.33	0.33	0.33	0.33	0.33	0.33	0.33
	Monthly monitoring cost (£'s)	**131**	**127**	**127**	**127**	**131**	**127**	**127**	**127**
	Total admin, pharmacy and monitoring cost / month	**713**	**1230**	**1881**	**2649**	**658**	**1153**	**1804**	**2572**

Table 50: Drug Costs

Product	mg/unit	Unit Price	£/mg
Folinic Acid non-proprietary			
3mg/ml * 1 amp	**3**	**2.28**	**0.7600**
3mg/ml * 10 amp	**30**	**4.62**	**0.1540**
7.5mg/ml * 2 amp	**15**	**7.8**	**0.5200**
10mg/ml * 5	**50**	**19.41**	**0.3882**
10mg/ml * 10	**100**	**35.09**	**0.3509**
10mg/ml * 30	**300**	**94.69**	**0.3156**
10mg/ml * 35	**350**	**90.98**	**0.2599**
Average per mg			0.3006
Oxaliplatin non proprietary			
50mg vial	**50**	**156.75**	**3.1350**
100mg vial	**100**	**313.5**	**3.1350**
Average per mg			3.1350
5FU non proprietary			
25mg/ml * 10	**250**	**3.2**	**0.0128**
25mg/ml * 20	**500**	**6.4**	**0.0128**
25mg/ml * 100	**2500**	**32**	**0.0128**
50mg/ml * 10	**500**	**6.4**	**0.0128**
50mg/ml * 20	**1000**	**12.8**	**0.0128**
50mg/ml * 50	**2500**	**32**	**0.0128**
50mg/ml * 100	**5000**	**64**	**0.0128**
Average per mg			0.0128
Capecitabine			
150mg * 60 tab	**9000**	**44.47**	**0.0049**
500mg * 120 tab	**60000**	**295**	**0.0049**
Average per mg			0.0049
Irinotecan			
2ml	**40**	**53.00**	**1.3250**
5ml	**100**	**130.00**	**1.3000**
15ml	**300**	**390.00**	**1.3000**
Average per mg			1.3023

Table 51: Adverse event costs taken from the 2007/8 reference costs

Currency Code	Currency Description	Activity	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost	Average Length of Stay - Days
EB10Z	Actual or suspected myocardial infarction	35,669	£381	£251	£439	1.00
EB10Z	Actual or suspected myocardial infarction	71,478	£1,523	£1,126	£1,757	5.36
PA23A	Cardiac Conditions with CC long-stay	2,250	£4,263	£2,088	£5,259	5.25
PA23B	Cardiac Conditions without CC long-stay	790	£1,932	£1,053	£2,361	3.11
PA23A	Cardiac Conditions with CC short-stay	949	£704	£362	£705	1.00
PA23B	Cardiac Conditions without CC short-stay	1,070	£488	£315	£565	1.00
Weighted Average Cardiac Event			1,201	852	1,392	4
EB11Z	Deep Vein Thrombosis long-stay	10,842	£1,339	£939	£1,597	5.07
EB11Z	Deep Vein Thrombosis short-stay	15,378	£320	£253	£370	1.00
Weighted Average Vein Thrombosis Event			741	537	878	3
PA45Z	Febrile Neutropenia with Malignancy long-stay	822	£3,024	£1,919	£3,652	5.13
PA45Z	Febrile Neutropenia with Malignancy short-stay	61	£554	£331	£698	1.00
Weighted Average Febrile Neutropenia Event			1,575	987	1,919	3
WA09W	Other non-viral infection with CC long-stay	2,044	£2,013	£1,294	£2,385	7.20
WA09Y	Other non-viral infection without CC long-stay	394	£1,400	£775	£1,696	4.39
PA16A	Major Infections with CC long-stay	1,151	£3,810	£2,191	£4,207	6.97
PA16B	Major Infections without CC long-stay	2,095	£2,215	£1,516	£2,694	4.63
PA17A	Intermediate Infections with CC long-stay	1,777	£1,897	£1,182	£2,231	3.71
PA17B	Intermediate Infections without CC long-stay	5,347	£1,299	£927	£1,585	2.71
PA18A	Minor Infections with CC long-stay	3,525	£1,591	£1,036	£1,921	3.26
PA18B	Minor Infections without CC long-stay	3,617	£1,137	£781	£1,448	2.45
PA16A	Major Infections with CC short-stay	336	£596	£364	£646	1.00
PA16B	Major Infections without CC short-stay	1,028	£532	£351	£620	1.00
PA17A	Intermediate Infections with CC short-stay	1,204	£473	£334	£578	1.00
PA17B	Intermediate Infections without CC short-stay	6,077	£460	£335	£550	1.00
PA18A	Minor Infections with CC short-stay	2,640	£463	£323	£575	1.00
PA18B	Minor Infections without CC short-stay	7,240	£451	£331	£540	1.00
WA09W	Other non-viral infection with CC short-stay	924	£378	£239	£465	1.00
WA09Y	Other non-viral infection without CC short-stay	373	£376	£254	£448	1.00
Weighted non Febrile Neutropenia Infection Event			1,077	721	1,292	2

Appendix E2: Personal Communication and Roche advisory board

Attendees of Roche Advisory board meeting Tuesday 09 June 2009

Chair
Professor Jim Cassidy (JC), Beatson Oncology Centre, Glasgow
Advisors
Dr John Bridgewater (JB), University College Hospital, London
Dr Ian Chau (IC), Royal Marsden Hospital, London
Dr Hugo Ford (HF), Addenbrooke's Hospital, Cambridge
Dr David Peake (DP), Queen Elizabeth Hospital, Birmingham
Dr Ian Pedley (IP), General Hospital, Newcastle
Dr Leslie Samuel (LS), Aberdeen Royal Infirmary
Professor Will Steward (WS), Leicester Royal Infirmary

Follow-up personal communication to elicit estimates for clinical practice assumptions were held with the following experts:

Dr John Bridgewater, University College Hospital, London
Professor Will Steward, Leicester Royal Infirmary
Professor Wagstaff, South West Wales Cancer Institute

Appendix E3: Probabilistic sensitivity analysis

For the parameters in listed in table 51, the Beta-Pert distribution was used assuming a minimum and maximum value of 50% and 150% of the mean respectively.

Table 52: Supportive care, adverse events, and pharmacy costs PSA parameters

	Low Estimate	Most-Likely Estimate	High Estimate
ADVERSE EVENTS			
cardiac disorders	852	1,201	1,392
Central line infection	721	1,077	1,292
Diarrhoea	190	237	284
Febrile Neutropenia	987	1,575	1,919
hypertension	173	200	237
infections (excl. Febrile neutropenia)	721	1,077	1,292
Neurotoxicity	14	18	22
Neutropenia / granulocytopenia	112	140	168
Palmar-plantar erythrodysaesthesia syndrome	110	137	164
Stomatitis	655	819	983
venous thromboembolism	537	741	878
Vomiting / Nausea	192	240	288
PROGRESSIVE DISEASE SUPPORTIVE CARE			
PROG	480	600	720
PHARMACY COSTS			
Pharmacy Complex infusion	33	42	50
Pharmacy Simple infusion / oral	20	25	30
Hospital transport one-way	45	56	67

Distribution = Beta Pert

Frequency of adverse events

Estimation of adverse event frequencies used in the PSA came from the beta distribution calculated as follows: BETAINV(RAND(),observed number of events, observed number of non-event).

Administration / Monitoring Costs

Estimates for administration and monitoring costs were sourced from the 2006/7 reference costs. The upper and lower quartiles from the reference costs were used to estimate the standard error and the gamma distribution was sampled from for the PSA

Table 53: Administration and monitoring PSA parameters

HRG Label	National Average Unit Cost	Lower Quartile (LQ)	Upper Quartile (UQ)	se
Patient Transport Services	£29.38	£20.16	£35.03	£11.02
District Nursing Services : Adult : Face To Face	£37.22	£24.52	£44.66	£14.93
Medical Oncology (Attendance without Treatment) Total Attendances	£125.14	£72.80	£161.42	£65.69
Deliver simple Parenteral Chemotherapy at first attendance	£219.22	£119.66	£289.30	£125.76
Deliver more complex Parenteral Chemotherapy at first attendance	£244.72	£127.96	£304.80	£131.09
Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	£317.28	£218.36	£419.65	£149.22
Deliver subsequent elements of a chemotherapy cycle	£227.10	£142.33	£286.56	£106.91
Vascular Access except for Renal Replacement Therapy with CC	£502.47	£258.07	£505.98	£183.77
Neoplasm diagnoses with length of stay 0 days	£1,052.17	£668.33	£1,263.37	£441.10

S.E. = (UQ-LQ)/(NORMINV(75%,0,1)*2)
PSA sampling distribution: Gamma

Utilities

The parameters for the distributions used for the probabilistic sensitivity analysis were calculated as follows: (beta (0.80 *1000, (1-0.80) *1000)

Kaplan-Meier PFS and OS curves

The transition probability for the element of the PFS and OS curves that are based on the Kaplan-Meier curves were calculated as follows: BETAINV(Rand(),number of event, number of non-events)

Exponential PFS extrapolation

Since the extrapolation is based on the gradient of the curve between months 13 and 29 the affect of changes in this part of the curve alters the extrapolation. Given that more than 93% of patients had progressed at the point that the extrapolation begins it was not deemed necessary to place a distribution around this element of the PFS curve above that affected by changes in the preceding Kaplan-Meier section of the curve.

Proportion of patients on treatment out of those remaining in PFS

A beta distribution was placed around this proportion for each monthly model cycle as follows: BETAINV(Rand(),number of event, number of non-events)

Weibull OS parameter estimates

Chemo + Bev

Deterministic Estimates	
Lambda (λ)	0.006119924
Gamma (γ)	1.547272063

	Estimate	StdErr
Intercept (μ)	3.18048342	0.02177147
Chemo + Bev	0.11318784	0.03851881
Scale (σ)	0.64629875	0.01587901

Chemo+-P

Deterministic Estimates	
Lambda (λ)	0.007291302
Gamma (γ)	1.547272063

Estimated Covariance Matrix Σ

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.000474	-0.000461	0.000039682
Chemo + Bev	-0.000461	0.001484	0.000042027
Scale (σ)	0.000039682	0.000042027	0.000252

Lower Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.021771541	0	0
Chemo + Bev	-0.021174431	0.032181415	0
Scale (σ)	0.001822655	0.002505194	0.015569263

Upper Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.021771541	-0.021174431	0.001822655
Chemo + Bev	0	0.032181415	0.002505194
Scale (σ)	0	0	0.015569263

Estimate Covariance Matrix (Σ=TT') - Validation step

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.000474000	-0.000461000	0.000039682
Chemo + Bev	-0.000461000	0.001484000	0.000042027
Scale (σ)	0.000039682	0.000042027	0.000252000

Z-Matrix (Std Normal random generated number)

Intercept (μ)	-1.482290342
Chemo + Bev	0.689903166
Scale (σ)	-0.19282675

Weibull PFS PSA parameter estimates

Chemo + Bev

Deterministic Estimates	
Lambda (λ)	0.0258572
Gamma (γ)	1.457360715

	Estimate	StdErr
Intercept (μ)	2.35224761	0.01998
Chemo + Bev	0.1558248	0.03361
Scale (σ)	0.68617192	0.01240

Chemo+-P

Deterministic Estimates	
Lambda (λ)	0.032449402
Gamma (γ)	1.457360715

Estimated Covariance Matrix Σ

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.000399	-0.000385	-0.000055407
Chemo + Bev	-0.000385	0.00113	0.000016806
Scale (σ)	-0.000055407	0.000016806	0.000154

Lower Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.019974984	0	0
Chemo + Bev	-0.019274108	0.027541038	0
Scale (σ)	-0.002773819	-0.001330992	0.012022245

Upper Triangular (Decomposition) Matrix (T)

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.019974984	-0.019274108	-0.002773819
Chemo + Bev	0	0.027541038	-0.001330992
Scale (σ)	0	0	0.012022245

Estimate Covariance Matrix (Σ=TT') - Validation step

	Intercept (μ)	Chemo+-P	Scale (σ)
Intercept (μ)	0.000399000	-0.000385000	-0.000055407
Chemo + Bev	-0.000385000	0.001130000	0.000016806
Scale (σ)	-0.000055407	0.000016806	0.000154000

Z-Matrix (Std Normal random generated number)

Intercept (μ)	0.042292433
Chemo + Bev	-0.169761962
Scale (σ)	-0.376442216

Parameter Estimates incorporating uncertainty (Mu + Tz)

Intercept (μ)	2.353092401
Chemo + Bev	0.15033423
Scale (σ)	0.681754879

PFS and OS Hazard Ratio for the FOLFIRI indirect comparison

PFS	mean HR	lower 95% CI	upper 95% CI	ln(mean HR)	ln(lower 95%)	ln(upper 95%)	s.e. (ln(HR))
FOLFIRI vs 5FU	**0.74**	0.66	0.83	-0.30	-0.42	-0.19	0.058
FOLFOX vs 5FU	**0.68**	0.59	0.77	-0.39	-0.53	-0.26	0.068
FOLFIRI vs FOLFOX	1.09	0.91	1.30	0.08	-0.09	0.26	0.090

OS	mean HR	lower 95% CI	upper 95% CI	ln(mean HR)	ln(lower 95%)	ln(upper 95%)	s.e. (ln(HR))
FOLFIRI vs 5FU	**0.91**	0.83	1.00	-0.09	-0.19	0.00	0.048
FOLFOX vs 5FU	**0.84**	0.74	0.94	-0.17	-0.30	-0.06	0.061
FOLFIRI vs FOLFOX	1.08	0.93	1.26	0.08	-0.07	0.23	0.077

The normal distribution based on the parameters above was used to sample generate the PSA result for survival analysis around the PFS and OS hazard rations for FOLFIRI compared to FOLFOX

Appendix E4: Post Protocol Treatments
NO16966

Table 13 Additional Anti-cancer Treatment Administered After Study Treatment Discontinuation and After Disease Progression (at least 2% in one arm) (4MSU ITT Population, NO16966)

Class/ Other Treatment or Procedure	FOLFOX-4 N = 317 No. (%)	FOLFOX-4+P N = 351 No. (%)	FOLFOX-4+BV N = 349 No. (%)	XELOX N = 317 No. (%)	XELOX+P N = 350 No. (%)	XELOX+BV N = 350 No. (%)
ALL CLASSES						
Total Pts with at Least one Treatment	201 (63)	250 (71)	217 (62)	182 (57)	230 (66)	215 (61)
Total Number of Treatments	636	851	711	548	732	651
TOPOISOMERASE INHIBITORS						
IRINOTECAN	156 (49)	195 (56)	176 (50)	140 (44)	186 (53)	169 (48)
ANTIMETABOLITES						
FLUOROURACIL	100 (32)	157 (45)	129 (37)	85 (27)	127 (36)	112 (32)
CAPECITABINE	59 (19)	49 (14)	53 (15)	45 (14)	35 (10)	40 (11)
RALTITREXED	3 (<1)	4 (1)	2 (<1)	1 (<1)	4 (1)	6 (2)
FOLIC ACID & DERIVATIVES						
FOLINIC ACID	87 (27)	137 (39)	102 (29)	74 (23)	107 (31)	93 (27)
CALCIUM LEVOFOLINATE	2 (<1)	4 (1)	7 (2)	-	4 (1)	1 (<1)
SURGICAL & MEDICAL PROCEDURES						
RADIOTHERAPY	46 (15)	50 (14)	34 (10)	37 (12)	52 (15)	39 (11)
HEPATECTOMY	2 (<1)	5 (1)	5 (1)	4 (1)	6 (2)	2 (<1)
MALIGNANT TUMOUR EXCISION	3 (<1)	4 (1)	4 (1)	1 (<1)	6 (2)	1 (<1)
RADIOFREQUENCY ABLATION	2 (<1)	2 (<1)	4 (1)	5 (2)	1 (<1)	1 (<1)
MONOCLONAL ANTIBODIES						
CETUXIMAB	38 (12)	67 (19)	60 (17)	34 (11)	64 (18)	56 (16)
PLATINUM COMPOUNDS						
OXALIPLATIN	28 (9)	32 (9)	27 (8)	22 (7)	32 (9)	28 (8)
ANGIOGENESIS INHIBITORS						
BEVACIZUMAB	24 (8)	35 (10)	26 (7)	29 (9)	33 (9)	24 (7)
CYTOTOXIC ANTIBIOTICS						
MITOMYCIN	15 (5)	20 (6)	15 (4)	11 (3)	16 (5)	19 (5)
ANTINEOPLASTIC AGENTS						
FLUOROURACIL/FOLINIC ACID/IRINOTECAN	3 (<1)	9 (3)	11 (3)	2 (<1)	5 (1)	8 (2)
FLUOROURACIL/FOLINIC ACID	4 (1)	1 (<1)	-	5 (2)	1 (<1)	2 (<1)

Percentages are based on N. trllap_6aa4001 (page 744), 13APR2007