NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Bevacizumab in combination with capecitabine for the treatment of metastatic breast cancer

December 2011

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Bevacizumab (Avastin®) is a recombinant humanised monoclonal antibody that binds to vascular endothelial growth factor (VEGF), a key driver of angiogenesis. This is a process vital to the survival and growth of tumours; neutralising the activity of VEGF both inhibits the formation of new tumour vasculature and regresses the existing tumour vasculature, thereby inhibiting tumour growth and survival.

Bevacizumab is approved for the following indications:

- in combination with fluoropyrimidine-based chemotherapy for treatment of patients with metastatic carcinoma of the colon or rectum
- in combination with paclitaxel or capecitabine for first-line treatment of patients with metastatic breast cancer
- in addition to platinum-based chemotherapy, for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology
- in combination with interferon alfa-2a for first line treatment of patients with advanced and/or metastatic renal cell cancer

Bevacizumab is available as a 25mg/ml solution for infusion. Two presentations are available, a 100mg vial (£242.66) and a 400mg vial (£924.40). The recommended dose in metastatic breast cancer is 10mg/kg every 2 weeks or 15mg/kg every three weeks, in combination with chemotherapy. Bevacizumab treatment is continued until disease progression. In clinical practice patients will only receive one course of treatment with bevacizumab.

Patients who present with metastatic breast cancer (mBC) have a number of treatment options; for treatment naive patients, an anthracycline or a taxane would usually be the standard of care. However, a majority of patients receive anthracycline therapy in the adjuvant setting for the treatment of their early breast cancer (eBC) and are then ineligible for further anthracycline therapy. Patients with eBC who have disease with a high risk of recurrence may, in addition, receive adjuvant taxane therapy before relapse. When patients relapse after receiving adjuvant taxane and

anthracycline therapy, they are often considered to be refractory to these therapies. These patients represent an acute unmet medical need in the treatment of mBC. They have already been treated with two of the most effective classes of chemotherapy and yet have recurrent disease which requires therapy. Capecitabine or vinorelbine are considered to be the most appropriate treatment options for such patients in the first-line metastatic setting. The introduction of bevacizumab + capecitabine combination therapy provides a much needed additional treatment option in this group of patients who are currently severely limited in their treatment options due to their lack of suitability for taxanes or anthracyclines.

Capecitabine (Xeloda®) is indicated for the treatment of metastatic breast cancer after the failure of taxanes and an anthracycline-containing regimen. Bevacizumab in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. This submission addresses the patient group covered by these two intersecting licensed indications, that is patients receiving first-line therapy for metastatic breast cancer, who have relapsed after receiving taxane and anthracycline adjuvant therapy (failed these regimens) and for whom further anthracycline or taxane therapy is not considered appropriate.

The submission is based on the results of the RIBBON-1 study. This is a randomised, double-blind, controlled, multi-centre, international study evaluating first-line chemotherapy in combination with bevacizumab versus chemotherapy with placebo in mBC patients who have relapsed >12 months after adjuvant chemotherapy. Investigators were able to select their choice of chemotherapy for patients entering this study, either anthracycline/taxane, or capecitabine, as in their routine clinical practice, before randomisation. The randomisation process then allocated patients to this chemotherapy plus bevacizumab or placebo. (Only the results from the capecitabine cohort of patients in this study provided a licensed indication for bevacizumab). Thus the patients in the capecitabine cohort were all considered unsuitable for anthracycline or taxane therapy; about 40% of the patients had also previously received taxane (and anthracycline) therapy for their eBC.

Overall, in the capecitabine cohort, RIBBON-1 demonstrated that the addition of bevacizumab to capecitabine as first-line therapy for locally recurrent or metastatic breast cancer resulted in a statistically significant and clinically meaningful improvement in PFS compared to capecitabine alone (HR = 0.69; log-rank p =

0.0002). The median PFS was 8.6 months for patients in the bevacizumab arm (n= 409) and 5.7 months for patients in the placebo arm (n=206). The median overall survival, unadjusted for use of bevacizumab post-progression, was 25.7 months with bevacizumab and 22.8 months with placebo (HR = 0.88, 95% CI: 0.69-1.12, p = 0.33). Two thirds of patients received bevacizumab post progression and this amount of cross over to bevacizumab may confound the overall survival results, as the study was not designed to evaluate the effect of subsequent therapies.

Subgroup analysis demonstrated that in the 245 patients who had relapsed with mBC after adjuvant taxane therapy, the median PFS more than doubled, from 4.2 months with capecitabine + placebo to 8.7 months with capecitabine + bevacizumab (HR= 0.62, 95% CI: 0.45-0.84). The 4.5 month PFS benefit observed in this subgroup of patients was also conveyed into a median overall survival benefit, of 7.9 months. The overall survival (unadjusted for post-progression bevacizumab) increased from 20.5 months in the patients who received capecitabine + placebo to 28.4 months with capecitabine + bevacizumab (HR = 0.67, 95%CI: 0.46-0.98), suggesting a statistically and clinically significant improvement in outcome in this group of patients for whom few therapeutic options are available.

The observed safety profile was in line with that seen in other breast cancer studies; no new safety signals were observed for bevacizumab.

Economic Summary

A cost utility analysis was conducted comparing bevacizumab in combination with capecitabine to capecitabine monotherapy in the subgroup of patients from RIBBON-1 who relapsed with mBC after adjuvant taxane therapy. The NICE reference-case was followed throughout (including the utilisation of 3.5% p.a. non-differential discounting, half cycle correction, an NHS/PSS perspective etc).

A 3 state model (progression free survival (PFS), progressed disease (PD) and death) was constructed in Excel with the proportion of patients in each health state derived directly from patient-level observations in the capecitabine (+/- bevacizumab) cohort of RIBBON-1 (after adjusting for post-progression bevacizumab use in both arms). Resource use in each health state was taken from CG81 (NICE CG81 2009). Costs were taken from BNF62, PSSRU 2010 and NHS Reference Costs 2009/2010 (Department of Health 2011;Joint Formulary Committee 2011;PSSRU 2010). The utilities used were those applied by Fleeman et al. (Fleeman et al. 2010) in the recent

assessment report for lapatinib and trastuzumab in combination with an aromatase inhibitor in HER2+/HR+ mBC (founded upon those derived by (Lloyd et al. 2006)).

The base-case results (after removing data for patients given bevacizumab post-progression) demonstrate that the addition of bevacizumab provides an additional 3.10 months mean progression-free survival and 10.4 months mean overall survival in a patient population in which typically survival is around 16.4 months (base-case results). Once quality adjusted this amounts to a QALY gain of 0.5034.

While the addition of bevacizumab offers patients with a high unmet clinical need a QALY gain of approximately 0.5, once combined with the incremental cost associated with bevacizumab (£38,856) the base-case results suggest that the incremental cost-effectiveness ratio of bevacizumab and capecitabine vs capecitabine alone in the prior-taxane treated cohort of RIBBON-1 is likely above that typically considered acceptable in the UK (at around £77,000 per QALY or £45,000 per life year gained).

Table 1: Base case cost-effectiveness results

	Bevacizumab + Capecitabine	**Capecitabine**
Technology acquisition cost Other costs	£33,452 £18,193	£1,714 £11,007
Total	**£51,645**	**£12,721**
Difference in total costs	**£38,856** **(Addition of bevacizumab is more expensive)**	
LYG	2.2283	1.3648
LYG difference	**0.8636** **(Addition of bevacizumab delivers health benefits)**	
QALYs	1.3381	0.8346
QALY difference	**0.5034** **(Addition of bevacizumab delivers health benefits)**	
ICER (Cost per QALY gained)	**£38,856/0.5034 = £77,318**	
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Section A – Decision problem

1 Description of technology under assessment

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

Avastin (bevacizumab). Pharmaco-therapeutic group. Antineoplastic agents, monoclonal antibody ATC code: L01X C07, BNF 8.1.5.

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

Bevacizumab is a humanised anti-vascular endothelial growth factor (VEGF) monoclonal antibody that inhibits VEGF-induced signalling and inhibits VEGF-driven angiogenesis. This reduces vascularisation of tumours, thereby inhibiting tumour growth.

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

Marketing authorisation was granted by EMA on 29th June 2011.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

On 16 December 2010, the CHMP had originally adopted a negative opinion on the use of Avastin in combination with standard cytotoxic chemotherapy (which included capecitabine), for the first-line treatment of patients with metastatic breast cancer (mBC). During the re-examination procedure, a proposed re-wording of the indication was presented to the committee:

“Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom other chemotherapy options are not preferred. Patients who have received taxane and anthracycline-containing regimen in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine”.

The committee considered that the indication should be more rigorously defined since preference alone is not informative in guiding patient selection and does not necessarily identify patients for whom other treatment options including taxanes and anthracyclines are not available. In response, the proposed indication was further revised, as follows:

‘‘Avastin in combination with capecitabine is indicated for first-line treatment of patients with metastatic breast cancer in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last 12 months should be excluded from treatment with Avastin in combination with capecitabine’’.

The committee concluded that in this patient population for whom there are limited therapeutic options, the modest increase in median PFS observed in the pivotal trial, AVF3694g (RIBBON-1), was clinically significant and should be assessed in this context. RIBBON-1was considered sufficiently robust to allow drawing meaningful conclusions in the revised proposed indication. In particular, the effect observed for bevacizumab and capecitabine was considered to be consistent across subgroups and robust to different assumptions explored in sensitivity analyses. The CHMP also concluded that although the addition of bevacizumab resulted in increased toxicity, this was not considered a major concern and is outweighed by a sufficient clinical benefit in terms of PFS for this restricted population.

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

Avastin, in combination with capecitabine, is indicated for first-line treatment of patients with mBC in whom treatment with other chemotherapy options including taxanes or anthracyclines is not considered appropriate. Patients who have received taxane and anthracycline-containing regimens in the adjuvant setting within the last

12 months should be excluded from treatment with Avastin in combination with capecitabine.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

RIBBON-1 (the pivotal trial supporting the extension of bevacizumab's licence to cover bevacizumab + capecitabine combination therapy) is the only completed study relevant to this appraisal. No other relevant studies are due to report in the next 12 months. The TURANDOT study is currently ongoing (capecitabine + bevacizumab vs paclitaxel + bevacizumab), data are currently immature and timelines for reporting are not defined – however, this study may be outside of scope for this appraisal given that patients enrolled are considered appropriate for receiving a taxane.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Bevacizumab was launched in the UK in 2005, following the granting of its first licensed indication in metastatic colorectal cancer.

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

Bevacizumab is licensed throughout the world for use in metastatic colorectal cancer (mCRC), advanced renal cell carcinoma (aRCC), advanced non-small cell lung cancer (aNSCLC) and in metastatic breast cancer (mBC).

CHMP positive opinion for the use of Avastin in advanced ovarian cancer (aOC) was received 23rd September 2011 (expected date of approval; November 2011).

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

An SMC submission for bevacizumab in this indication will commence in approximately January 2012 with guidance expected in June 2012.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 1: Unit costs of technology being appraised

Pharmaceutical formulation	Bevacizumab is available in two vial sizes. A 4ml vial containing 100mg of bevacizumab and a 16ml vial containing 400mg of bevacizumab.
Acquisition cost (excluding VAT)	100mg/4ml vial: £242.66 400mg/16ml vial: £924.40
Method of administration	Bevacizumab is administered by intravenous infusion.
Doses	In mBC bevacizumab is administered at 15mg/kg at each dose until disease progression or unacceptable toxicity.
Dosing frequency	Every 21 days.
Average length of a course of treatment	In RIBBON-1 patients in the capecitabine arms received a mean of just over 11 cycles of bevacizumab.
Average cost of a course of treatment	£30,840 – Cost of bevacizumab (including wastage) in base-case economic analysis.
Anticipated average interval between courses of treatments	An mBC patient will receive only one course of treatment with bevacizumab.
Anticipated number of repeat courses of treatments	An mBC patient will receive only one course of treatment with bevacizumab.
Dose adjustments	The dose of bevacizumab is not reduced or escalated. In cases of serious bevacizumab-related toxicity, bevacizumab may be either temporarily or permanently discontinued.

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

N/A

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

No additional tests are required to select patients for the administration of bevacizumab and no additional tests are required prior to the administration of bevacizumab. Treatment with bevacizumab should continue until disease progression, which will be determined in the usual manner for mBC patients. A small amount of additional resource will be required for the administration of bevacizumab alongside the patient's routine cytotoxic chemotherapy.

There will be minimal additional monitoring to that required for a patient's chemotherapy, to detect the most common side effects of bevacizumab.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The introduction of bevacizumab into the care pathway warrants minimal additional monitoring above and beyond current clinical practice in first line mBC.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

In RIBBON-1 bevacizumab was given in combination with capecitabine 1000mg/m^2 twice daily on the first 14 days of each 21 day cycle.

2 Context

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Breast cancer is the most common cancer in women worldwide with around 1.38 million women diagnosed in 2008; the highest rate of occurrence is in Western Europe and North America. In 2008 39,681 new cases of breast cancer were diagnosed in women in England alone (Cancer Research UK 2009). There were 10,065 deaths from breast cancer in England in 2008 with breast cancer currently accounting for around 16% of female deaths in the UK.

Death from breast cancer is a consequence of metastatic disease, which is estimated to be present in 5-10% of women at the time of first presentation, metastatic disease will also affect 30-40% of patients initially diagnosed with early or localised breast cancer confined to the breast and its draining lymph nodes (Burstein, Harris, & Morrow 2008;NICE CG81 2009;O'Shaughnessy 2005).

Heterogeneity of response in metastatic patients

The median time from diagnosis with metastatic disease to death is reported to be about 2 years (IARC 2003), but such median figures hide considerable heterogeneity. For example, post-menopausal women with tumours bearing large numbers of both oestrogen and progesterone hormone receptors (ER, PgR) typically have disease that follows a relatively indolent course and these patients may survive for a prolonged period of time (Anderson, Jatoi, & Devesa 2005;Muss, Smith, & Cooper 1987;Ravdin et al. 1992).

Other patients with more aggressive forms of the disease have a poorer prognosis with higher risk of early relapse and short overall survival. Human epidermal growth factor receptor 2 (HER2) negative breast cancer patients with such a poor prognosis represent a very significant unmet medical need for new therapies. These patients tend to relapse rapidly after their response to first-line therapy and have a short overall survival, due to a lack of durable response to subsequent therapies. Although a number of different patient types may be assigned to the ‘high risk of poor prognosis’ group, in general they include patients with triple negative disease (they lack hormonal receptors ER and PR, as well as the *HER2/neu* gene), with positive

lymph nodes at diagnosis, a high grade histology, or who have previously received prior taxane and anthracycline treatment.

Taxane pre-treated patients

A group of patients who currently represent an acute unmet medical need in the treatment of mBC are HER-2 negative patients treated with an anthracycline plus taxane therapy in the adjuvant setting. Such patients have already been treated with two of the most effective classes of neoadjuvant/adjuvant chemotherapy and yet have recurrent disease which requires therapy; disease in this setting may often be rapidly-growing aggressive disease, as indicated by the need to treat such patients with a taxane in the adjuvant setting. Such patients are ineligible for further anthracycline therapy and they are likely to be at least partially resistant to taxane therapy. To date, there are no specific NICE recommendations for the treatment of this population of patients (see section 2.4 for full details of treatment pathway).

Capecitabine therapy is a common treatment for patients who have previously received a taxane. Capecitabine monotherapy is specifically licensed for the treatment of mBC after failure of taxanes and an anthracycline-containing regimen (Xeloda SPC 2011). Approximately half of patients in the UK will receive first-line capecitabine monotherapy if they are not eligible for a taxane or anthracycline treatment i.e. those that have received the full maximum anthracycline dose, have relapse after adjuvant taxane, and those that cannot tolerate either treatment (Data on File, RXUKDONF00118).

Treatment Objectives of mBC

The treatment of mBC typically consists of the sequential challenge of a series of treatments with the intention of shrinking the size of the tumour. Unfortunately, the benefits of treatment in this setting tend not to be long term and response rates and the duration of response decline with each successive line of treatment (Burstein, Harris, & Morrow 2008;Jones 2008;Wood et al. 2005). Cancer survivors whose disease recurs have a lower quality of life in most quality of life indices than those who remain disease-free (Helgeson & Tomich 2005) and the most important distress factor among cancer survivors was found to be the fear of disease progression (Herschbach et al. 2004). Therefore, the major objective of each successive line of therapy is to increase the proportion of patients who respond to first-line therapy and to prolong their disease remission.

Choice of cytotoxic treatment

For women who are not candidates for hormonal therapy and whose tumours are HER2 -ve, cytotoxic chemotherapy is still the treatment of choice for locally advanced or metastatic disease. Existing monotherapy treatments such as anthracyclines, taxanes, vinca alkaloids, and anti-metabolites such as capecitabine, are used in the first-line metastatic setting and are capable of prolonging both disease-free and overall survival. Combination of these cytotoxic drugs provides a higher objective response rate (ORR) and a longer progression free survival (PFS) compared to monotherapy treatments; however, the gains of combination treatment generally come at the expense of increased side effects and overlapping toxicities. As a result, the use of sequential single agent cytotoxic chemotherapy remains a frequent approach.

In patients who have received an anthracycline and taxane in the adjuvant setting, treatment choices are potentially more limited, as patients may have acquired resistance to taxane therapy, resulting in poor outcomes when re-treated with a taxane in the metastatic setting. Having used two of the most effective treatment options in the adjuvant setting, these patients are often left with less efficacious monotherapy treatment options such as capecitabine and vinorelbine. Therefore, there is a large unmet clinical need to provide effective doublet treatment to first line metastatic patients who have already received two of the most effective treatments for breast cancer.

The clinical need for improved therapeutic efficacy

Increasing the benefit provided in the first-line metastatic setting, by raising the response rate and extending PFS, should significantly improve the therapeutic outcome for patients. Inevitably, combinations of cytotoxic agents show an increase in toxicities such as neutropenia, neuropathy and diarrhoea. Targeted biological agents can offer a significant increase in response rate and PFS; though do not add significantly to the patients' burden of toxic side-effects. Biological agents could be considerably valuable in this setting.

A challenge facing oncologists in the UK is how to manage patients presenting with metastatic disease who have been treated in the adjuvant setting with taxanes and/or anthracyclines, as currently, clinicians have a very limited armoury of therapies with which to treat such patients and their outlook may be very poor.

2.2 How many patients are assumed to be eligible? How is this figure derived?

The annual incidence of mBC in England and Wales is 10,913. This is calculated from the total population (Office of National Statistics 2011a;Office of National Statistics 2011b) and the age-standardised incidence rate of breast cancer (Cancer Research UK 2011). Approximately 32% of mBC patients receive taxanes in an adjuvant setting (Roche Data on File 2011) and a further 76% are HER2 –ve (Roche Data on File 2011). Of the 2,654 patients remaining, 72% are treated with chemotherapy (Roche Data on File 2011), 92% of these are not enrolled in a clinical trial (Roche Data on File 2011), 55% are treated with capecitabine (monotherapy or in combination with another agent) (Roche Data on File 2011) and 96% are not contraindicated for bevacizumab (Scarborough et al. 2010). We assume that 83% of patients fulfilling these criteria have relapsed more than 12 months after initial anthracycline and taxane treatment (Dent et al. 2007). Thus the total annual number of patients expected to be eligible for bevacizumab in this indication is approximately 773.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

NICE have issued guidance on the treatment of HER2 negative mBC in NICE TA30 (taxanes – replaced by NICE CG81), NICE TA54 (vinorelbine – replaced by NICE CG81), NICE TA62 (capecitabine – replaced by NICE CG81), NICE TA116 (gemcitabine) and in the NICE advanced breast cancer clinical guidelines (NICE CG81) (NICE CG81 2009). Subgroups relevant to this submission were not discussed in CG81. NICE have also issued guidance on the treatment of HER2 negative mBC with bevacizumab in combination with a taxane (TA214), where bevacizumab and taxanes were not recommended for the first-line treatment of mBC.

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There are currently no specific NICE recommendations for patients with mBC who have been given both anthracycline and taxane as prior adjuvant therapy.

The current NICE guidelines for the treatment of both early breast cancer (NICE 2009) and mBC (NICE CG81 2009) recommend that HER2 negative, anthracycline naïve patients for whom treatment with anthracyclines is appropriate should receive anthracyclines as the first option of invasive breast cancer treatment. For patients with early breast cancer, NICE CG80 states that:- “anthracycline containing regimens have been used routinely in the adjuvant setting” (NICE 2009).

CG80 goes on to recommend that docetaxel can be offered to patients with lymph node-positive breast cancer as part of an adjuvant chemotherapy regimen (NICE 2009). If a patient relapses with metastatic disease once they have received the given anthracycline dose (or they are not suitable for anthracycline treatment) NICE CG81 recommends patients should be offered single-agent docetaxel, followed by single-agent vinorelbine or capecitabine (NICE CG81 2009).

CG81 does not make any recommendation for patients with mBC who have been given both anthracycline and taxane as prior adjuvant therapy (NICE CG81 2009). It is well recognised by clinicians that for such patients, when they relapse after taxane adjuvant therapy, the outcomes of taxane treatment in the metastatic setting may be very poor. If patients are unable to tolerate a taxane or have relapsed from adjuvant taxane therapy the next available first line treatment options are capecitabine or vinorelbine monotherapy. It is this patient group for whom the combination of capecitabine and bevacizumab is intended.

The addition of bevacizumab to standard capecitabine monotherapy treatment is not anticipated to cause a major shift in the care pathway. As previously mentioned, the Xeloda (capecitabine) SPC specifies capecitabine monotherapy for the first-line treatment of mBC after failure of taxanes and an anthracycline-containing regimen (Xeloda SPC 2011). With approximately half of patients (who are not eligible for a taxane or anthracycline treatment) receiving first-line capecitabine monotherapy in the UK (Data on File, RXUKDONF00118, capecitabine remains one of the most widely used treatments for patients unsuitable for taxane or anthracycline treatment.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

N/A (Currently there are not specific guidelines for patients who have received a prior anthracycline and taxane)

2.6 Please identify the main comparator(s) and justify their selection.

Market research (Data on File, RXUKDONF00118)(Roche Data on File 2011) has indicated that the majority of HER2 –ve patients previously treated with anthracyclines and taxanes receive capecitabine monotherapy. According to the same research, vinorelbine is used far less often and therefore we consider capecitabine monotherapy to be the most appropriate comparator in this setting.

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Anti-hypertensives, agents used to manage congestive heart failure angiotensin-converting enzyme inhibitors, diuretics and calcium channel blockers.

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Bevacizumab is intravenously administered in a hospital setting every 21 days. This administration requirement equates to a cost of £271 per cycle (NHS Reference costs 2009/2010 (SB13Z): Deliver more complex Parenteral Chemotherapy at first attendance (Daycase)) for the first administration of chemotherapy (Department of Health 2011). Subsequent cycles of chemotherapy are associated with a tariff of £128 (NHS Reference costs 2009/2010 (SB97Z): Same day Chemotherapy admission/attendance (Daycase and Regular Day / Night))(Department of Health 2011). In addition to this delivery cost bevacizumab will require pharmacy preparation of infusion every 21 days.

2.9 Does the technology require additional infrastructure to be put in place?

No.

3 Equity and equality

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

To Roche's knowledge there are no such issues.

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

No such issues are anticipated.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

N/A

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with HER2-negative metastatic breast cancer previously untreated in the metastatic setting: for whom treatment with other chemotherapy options, including taxanes or anthracyclines, is not considered appropriate and who have not received taxane or anthracycline-containing regimens in the adjuvant setting within the last 12 months	As per scope	We have interpreted the capecitabine licence "after failure of taxanes and an anthracycline-containing regimen" as indicating the **subgroup** of patients who have previously received a taxane in the adjuvant setting (and have most likely also received an anthracycline in the adjuvant setting) from the RIBBON-1 capecitabine arm. While all patients in the RIBBON-1 capecitabine cohort will have been considered unsuitable for taxanes and anthracyclines as their 1st line mBC therapy, it is not possible to identify the patients given prior taxane and anthracyclines from the ITT capecitabine arm cohort.
Intervention	Bevacizumab in combination with capecitabine	As per scope	
Comparator (s)	Capecitabine monotherapy Vinorelbine monotherapy	As per scope	Vinorelbine is not a common therapy used in this setting, however, based on NICE CG81 (NICE CG81 2009), we will conduct an indirect comparison against vinorelbine by assuming identical outcomes to capecitabine monotherapy but drug costs specific to vinorelbine.
Outcomes	The outcome measures to be considered include: 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	As per scope	

	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.		
Subgroups to be considered	Potential subgroups such as by histology and hormone receptor status will be considered if evidence allows.	As per scope	Please see comment on Population above. Our submission has focused on a subgroup from the RIBBON-1 RCT which reflects our licensed population.
Special considerations, including issues related to equity or equality	None	As per scope	

Section B – Clinical and cost effectiveness

5 Clinical evidence

5.1 Identification of studies

5.1.1 **Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be 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 section 9.2, appendix 2.**

Searches used index and text words which included bevacizumab, capecitabine and breast cancer as descriptors. The search was restricted to include only documents relating to humans and clinical trials, and excluded reviews wherever possible. Only publications written in English were assessed. Where possible the search was restricted to metastatic or advanced breast cancer. The search was further restricted manually according to inclusion/exclusion criteria in Section 9.2.6.

Full details of the searches conducted and terms used are provided in Appendix 9.2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in Section 9.2.7.

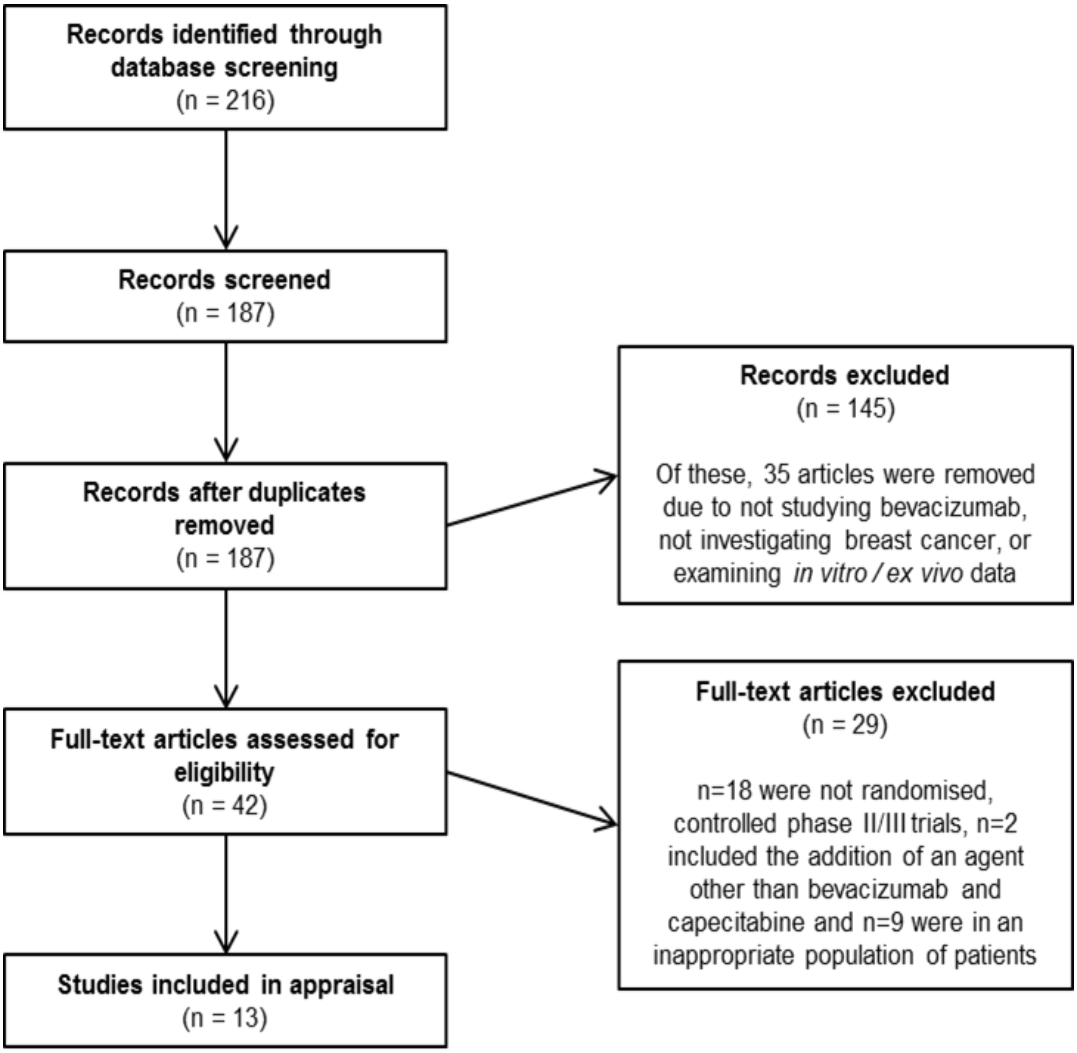
5.2 Study selection

5.2.1 **Inclusion and exclusion criteria**

See section 9.2.6

5.2.2 **Flow diagram of the number of studies included and excluded at each stage**

Figure 1: PRISMA Statement Flow Diagram



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

The references relevant to the specific studies are listed under the study heading.

5.2.4 **Provide details 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 Evidence Review Group.**

Table 2: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Trial 1 RIBBON-1	Bevacizumab in combination with chemotherapy: capecitabine n=615); a taxane (n=307), or an anthracycline (n=315) (Capecitabine 1,000mg/m^2 orally twice daily on days 1–14 every 3 weeks plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks.)	Chemotherapy alone with placebo	n=1237 Patients with locally recurrent or untreated mBC	The full study was published by Robert et al. Robert et al. RIBBON-1: randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011 1: 29 (10); 1252-1260.
Trial 2 TURANDOT	Capecitabine 1,000mg/m^2 orally twice daily on days 1–14 every 3 weeks plus bevacizumab 15mg/kg i.v. on day 1 every 3 weeks.	Paclitaxel 90mg/m^2 i.v. on days 1, 8 and 15 every 4 weeks plus bevacizumab 10mg/kg i.v. on days 1 and 15 every 4 weeks	No prior chemotherapy for locally recurrent or metastatic disease.The recruitment target is enrolment of 560 patients within 18 months.	Four abstracts have been presented, outlining the study design and preliminary safety findings.

RIBBON-1

The RIBBON-1 study (AVF3694g) is a multi-centre, double blind, phase III, randomised, placebo-controlled trial to evaluate the efficacy and safety of bevacizumab in combination with chemotherapy (taxane, anthracycline-based and capecitabine) compared with chemotherapy alone in patients with locally recurrent or untreated MBC.

The following articles and abstracts have been published:

Dieras V et al. Efficacy in patient subgroups in RIBBON-1, a randomized, double-blind, Phase III trial of chemotherapy with or without bevacizumab (B) for first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). Eur J Cancer Suppl 2009; 7(2): 265.

Robert N et al. RIBBON-1: Randomized, double-blind, placebo-controlled, Phase III trial of chemotherapy with or without bevacizumab (B) for 1st-line treatment of HER2-negative locally-recurrent or metastatic breast cancer (MBC). J Clin Oncol 2009; 27:15s (suppl), Abstract 1005 and Oral Presentation.

Robert N et al. Clinical benefit rate and time to response in RIBBON-1, a randomized, double-blind, phase III trial of chemotherapy with or without bevacizumab (B) for the first-line treatment of HER2-negative locally recurrent or metastatic breast cancer (MBC). Cancer Res 2009; 69: 851s, Abstract 6084.

Dieras V et al. Efficacy of first−line capecitabine plus bevacizumab in patients with ER/PgR−positive metastatic breast cancer (MBC) and those previously treated with hormone therapy. Eur J Cancer supplements 2010 8: 202

Brufsky A et al. Influence of disease free interval on the efficacy of capecitabine−bevacizumab for HER2−negative metastatic breast cancer (MBC) in the RIBBON−1 trial. EJC Supplements, 2010, vol. 8, no. 3, p. 201,

Bondarenko I et al. PFS by patient subgroup for standard chemotherapies in combination with bevacizumab (BV) in the first−line treatment of HER2−negative locally recurrent (LR) or metastatic breast cancer (mBC): results from RIBBON−1. EJC Supplements, 2010, vol. 8, no. 3, p. 198

O'Shaughnessy J et al. Consistent progression−free survival benefit of capecitabine−bevacizumab in all prespecified subgroups of the RIBBON−1 study in patients with metastatic breast cancer (MBC). EJC Supplements, 2010, vol. 8, no. 3, p. 198.

Lindman et al. RIBBON-1: efficacy of capecitabine-bevacizumab in patients with triple-negative metastatic breast cancer (MBC). EJC Supplements 2010, vol. 8, no. 3, p. 204,

Robert et al. RIBBON-1: Randomized, double-blind, placebo-controlled, phase III trial of chemotherapy with or without bevacizumab for first-line treatment of human epidermal growth factor receptor 2-negative, locally recurrent or metastatic breast cancer. J Clin Oncol 2011. 29:10; 1252-1260.

TURANDOT

The Central European Cooperative Oncology Group (CECOG) TURANDOT study is an ongoing phase III, randomised, open-label, parallel-group trial designed to determine the relative efficacy of bevacizumab plus capecitabine versus bevacizumab plus paclitaxel as first-line therapy in patients with locally recurrent or MBC.

Lang I et al. Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first−line therapy for HER2−negative locally recurrent or metastatic breast cancer (LR/MBC): the CECOG phase III TURANDOT trial. EJC Supplements, 2009, vol. 7, no. 2, p. 277−278,

Lang I et al. Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first-line chemotherapy (CT) for HER2-negative, locally recurrent or metastatic breast cancer (LR/MBC): Preliminary safety data from the CECOG phase III TURANDOT trial. J Clin Oncol 2010: 28:15s, suppl; abstr 1126.

Inbar M et al Randomized Phase III Study of First-line Bevacizumab in Combination With Capecitabine or Paclitaxel for HER2-negative LR/MBC: Interim Safety Data", EJC vol. 2011 47, no. Suppl. 1, p. S346

Lan et al. Safety subgroup analyses from the CECOG phase III TURANDOT trial: first-line bevacizumab (BEV) in combination with capecitabine (X) or paclitaxel (P) for HER2-negative locally recurrent or metastatic breast cancer (LR/MBC). Annals of Oncology 2010, 21: 8; 1281PD

5.2.5 **Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.**

RIBBON-1 (AVF3694g) is the only study that compares the intervention directly with the appropriate comparators.

5.2.6 **When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.**

Studies excluded from potentially relevant randomized controlled trials

Records for the RCTs listed below were obtained in full for further investigation. These records were excluded based on exclusion criteria listed in section 9.2.6. A brief discussion of the rationale for excluding each study is provided above the relevant reference citations.

TURANDOT

Recruitment for this trial is ongoing, and only preliminary safety data has been presented at ASCO 2010, for 167 patients. No efficacy data is available currently, and therefore this trial is excluded from further discussions according to exclusion criterion 5.

Lang I et al. Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first−line therapy for HER2−negative locally recurrent or metastatic breast cancer (LR/MBC): the CECOG phase III TURANDOT trial. EJC Supplements, 2009, vol. 7, no. 2, p. 277−278,

Lang I et al. Bevacizumab (Bev) combined with either capecitabine (X) or weekly paclitaxel (Pac) as first-line chemotherapy (CT) for HER2-negative, locally recurrent or metastatic breast cancer (LR/MBC): Preliminary safety data from the CECOG phase III TURANDOT trial. J Clin Oncol 2010: 28:15s, suppl; abstr 1126.

Inbar M et al Randomized Phase III Study of First-line Bevacizumab in Combination With Capecitabine or Paclitaxel for HER2-negative LR/MBC: Interim Safety Data", EJC vol. 2011 47, no. Suppl. 1, p. S346

Lan et al. Safety subgroup analyses from the CECOG phase III TURANDOT trial: first-line bevacizumab (BEV) in combination with capecitabine (X) or paclitaxel (P) for HER2-negative locally recurrent or metastatic breast cancer (LR/MBC)". Annals of Oncology 2010, 21: 8; 1281PD

List of relevant non-RCTs

5.2.7 **Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table.**

Non-relevant RCTs were not assessed in this submission

5.3 Summary of methodology of relevant RCTs

5.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

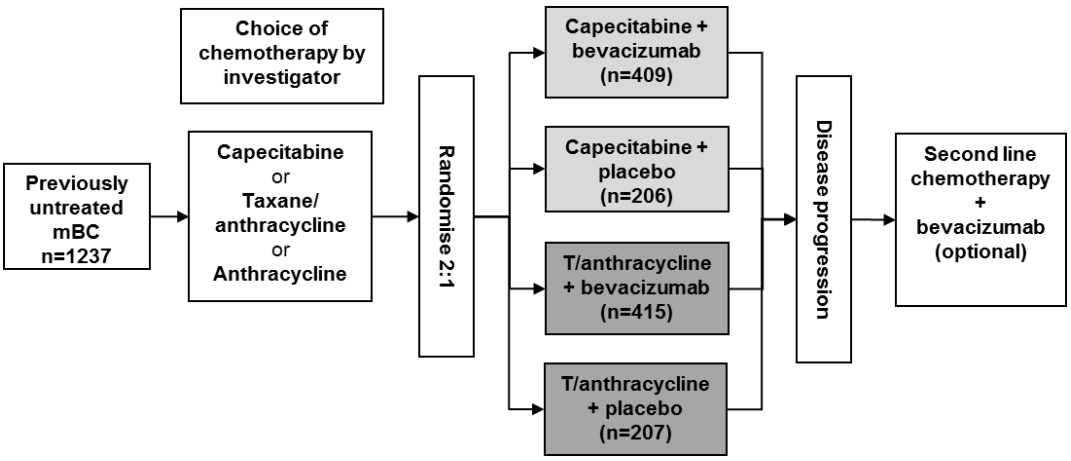
Methods

5.3.2 **Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.**

Summary of the RIBBON-1 (AVF3694g) study

RIBBON-1 was an international, multicentre, double blind, phase III, randomised, placebo-controlled trial to evaluate the efficacy and safety of bevacizumab in combination with chemotherapy compared with chemotherapy alone in patients with locally recurrent or untreated metastatic breast cancer (Figure 2).

Figure 2: Study Schema RIBBON-1



Treatments included:

- Bevacizumab or placebo 15mg/kg every 3 weeks
- Capecitabine 1000mg/m^2 twice daily on day 1-14 followed by a 7 day break.
- Taxane (docetaxel 75–100 mg/m^2 or nab-paclitaxel 260 mg/m^2) every three weeks.
- Anthracycline-based chemotherapy:
    - AC (doxorubicin 50–60 mg/m^2, cyclophosphamide 500–600 mg/m^2),
    - EC (epirubicin 90–100 mg/m^2, cyclophosphamide 500–600 mg/m^2),
    - FAC (5-FU 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2),
    - FEC (5-FU 500 mg/m^2, epirubicin 90–100 mg/m^2, cyclophosphamide 500 mg/m^2)

RIBBON-1: 1237 patients were enrolled and randomised in a 2:1 ratio to receive chemotherapy + bevacizumab or chemotherapy + placebo. The trial investigates two separate, individually powered cohorts of patients, the arms of the trial test two distinct scientific hypotheses therefore allowing data to be analysed separately.

Patients were enrolled into the two different cohorts of the study according to the clinician's choice of cytotoxic therapy, reflecting the choice of first-line therapy made for such patients in routine clinical practice.

Following determination of eligibility patients in the capecitabine cohort were enrolled at 178 investigative sites: 309 patients were enrolled at 113 sites in the United States, and 306 patients were enrolled at 65 sites outside the United States.

A placebo control for bevacizumab was employed to minimise bias in the assessment of disease progression and adverse event reporting. PFS was chosen as the primary endpoint to assess the clinical benefit of bevacizumab in combination with chemotherapy in this disease setting. To further evaluate efficacy, secondary endpoints including response rate, duration of response, overall survival, and 1-year survival rate were assessed. The study also assessed the toxicity profile of the addition of bevacizumab to capecitabine in previously untreated patients with mBC.

An IRC assessment of the primary endpoint of PFS was added as a sensitivity analysis to provide additional support for the primary endpoint of investigator-assessed PFS. The IRC for this study used radiologic and clinical evidence to detect tumor progression in a retrospective manner. Imaging-based evaluation by the IRC was performed by two radiologists and adjudicated by a third radiologist if necessary. The reviews were performed in a blinded fashion.

To test the consistency of treatment benefits with respect to the primary efficacy endpoint, progression free survival and overall survival was calculated in many important subgroups. These include prior taxane therapy, prior anthracycline therapy, triple negative status, age, race, baseline ECOG performance status (0 vs. 1),menopausal status, number of metastatic sites, sites of involvement, disease measurability, SLD of target lesions, HR status, disease-free interval, prior neoadjuvant/adjuvant chemotherapy, prior adjuvant hormone therapy, prior hormonal therapy for locally recurrent or metastatic disease.

Treatment duration and follow up

This study began patient accrual in December 2005 with the data cutoff in July 2008. This study included a blinded treatment phase, an optional open-label post-progression phase, and a survival follow-up phase. During the blinded treatment phase, patients received chemotherapy and study drug (bevacizumab or placebo) every 3 weeks until disease progression, treatment-limiting toxicity, or death due to any cause. The optional open-label post-progression phase consisted of treatment that included chemotherapy (per investigator discretion) and bevacizumab. A maximum of 48 months of treatment with bevacizumab (blinded treatment phase plus optional open-label post-progression phase) was allowed. Patients who completed the study or who were discontinued from treatment (regardless of participation in the optional open-label post-progression phase) were followed for survival and subsequent anti-cancer therapies every 4 months until death, withdrawal of consent, loss to follow-up, or study termination. Patients who discontinued from treatment during the blinded treatment phase for reasons other than disease progression were followed with tumor assessment every 9 weeks, until documented disease progression, death or completion of study unblinding.

Bevacizumab Dosage

Bevacizumab dosage in the blinded treatment phase

The dose of bevacizumab was 15mg/kg by IV infusion every 3 weeks until disease progression. The dose of bevacizumab was based on the patient's weight and remained the same throughout the blinded treatment phase of the study. Patients who did not experience disease progression were allowed to receive a maximum duration of study drug (bevacizumab/placebo) therapy of 48 months. Patients continued to receive study drug when chemotherapy was discontinued prior to disease progression.

Bevacizumab dosage in the optional open-label post-progression phase

For patients in either treatment arm who received second-line therapy following disease progression, bevacizumab was administered at either 15 mg/kg IV every 3 weeks or 10 mg/kg IV every 2 weeks, in accordance with the frequency of administration of the concomitant chemotherapy agents. The dose of bevacizumab was based on the patient's weight at the start of the optional open-label post-progression phase and remained the same throughout this phase of the study. Bevacizumab was administered until disease progression, unacceptable toxicity, investigator decision, completion of 48 months of bevacizumab therapy (during the blinded treatment phase and optional open-label post-progression phase combined), or death.

Dose omission or modification of bevacizumab

There were no reductions in bevacizumab/placebo dose in this study. If an adverse event occurred that necessitated holding bevacizumab/placebo, the dose remained unchanged once treatment resumed.

Dosage of Protocol-Allowed Chemotherapy

As marketing authorisation for the technology only includes the capecitabine cohort of the trial, this arm of the study will be the focus of this document.

Dosage during the Blinded Treatment Phase

At study entry, the choice of chemotherapy was declared prior to randomisation and was selected at the investigator's discretion. Capecitabine was given at a dose of 1000mg/m^2, twice daily for two weeks of a three week cycle until disease progression, unacceptable toxicity, investigator/patient decision, or death, whichever occurred first. Patients continued to receive capecitabine if study drug was discontinued prior to disease progression.

Dosage during the Optional Open-Label Post-Progression Phase

The type of chemotherapy administered during the optional open-label post-progression phase was based on investigator's discretion. No anthracycline therapy was allowed. Other investigational therapies were not allowed prior to discontinuation of bevacizumab. Dose modifications for all chemotherapy agents were allowed at the investigator's discretion. Chemotherapy during the optional open-label post-progression phase was continued until disease progression, unacceptable toxicity, investigator/patient decision, or death, whichever came first.

Administration of Protocol-Allowed Chemotherapy

Capecitabine was administered according to the respective prescribing information or institutional practice. Once randomisation occurred, no substitutions of chemotherapy agents were made prior to documented disease progression unless the decision to discontinue the protocol-specified chemotherapy and initiate an alternative regimen was made for reasons of chemotherapy intolerance. Such decisions had to be made within the first 30 days of protocol-specified therapy.

Dose Omission or Modification of Protocol-Allowed Chemotherapy

Dose modification for any chemotherapy agents was implemented according to respective institutional practice and prescribing information.

Blinding

Roche (Genentech), investigators, and patients were blinded to the assignment of bevacizumab or placebo. Optional unblinding was allowed if a patient had documented progressive disease and if such information determined the next course of treatment.

Randomisation

Choice of chemotherapy was declared prior to randomisation and was based on the investigator's discretion per institutional standards. After written informed consent was obtained and eligibility was established, the study site obtained the patient's identification number and randomisation to treatment arm from the IVRS.

Randomisation was stratified by the following criteria:

- Disease-free interval (≤12 months, >12 months since completion of adjuvant chemotherapy, or surgery if no adjuvant chemotherapy)

- Prior adjuvant chemotherapy (yes, no)
- Number of metastatic sites (<3, ≥3)
- Choice of chemotherapy (taxane, anthracycline-based, capecitabine)

Outcomes

The primary efficacy endpoint of the study was progression-free survival (PFS) based on investigator assessment.

Secondary efficacy endpoints were overall survival, 1-year survival rate, objective response rate in patients with measurable disease, duration of objective response, and PFS based on Independent Review Committee (IRC) assessment. For scoring assessments and analysis timings see section 5.3.8.

The study consisted of two independently powered analysis cohorts:

- the taxane or anthracycline chemotherapy cohort
- the capecitabine cohort

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial.

Table 3: Inclusion Criteria

Inclusion Criteria	Histologically or cytologically confirmed adenocarcinoma of the breast, with measurable or non-measurable locally recurrent or metastatic disease (per RECIST criteria). Locally recurrent disease must not have been amenable to resection with curative intent. Signed Informed Consent Form Age ≥ 18 years For women of childbearing potential, use of accepted and effective method of non-hormonal contraception ECOG performance status of 0 or 1 Ability to comply with study and follow-up procedures.

Table 4: Exclusion Criteria

Exclusion Criteria	Disease and Treatment History HER2-positive status: HER2-positive patients were eligible only if they received prior treatment with trastuzumab, unless trastuzumab therapy was contraindicated or unavailable Prior chemotherapy for locally recurrent or metastatic disease Prior hormonal therapy 1 < week prior to locally recurrent or metastatic disease was allowed. Prior adjuvant or neo-adjuvant chemotherapy within 12 months prior to Day 0 Investigational therapy within 28 days of Day 0 Major surgery within 28 days prior to day 0 or minor surgery within 7 days of day 0. Prior therapy with bevacizumab, sorafenib, sunitinib, or other VEGF pathway-targeted therapy Patients had to recover by day 0 from any grade ≥3 radiation Bevacizumab Exclusion Criteria Known brain or other CNS metastases Blood pressure >150/100 mmHg Unstable angina New York Heart Association (NYHA) Grade II or greater congestive heart failure History of myocardial infarction (within last 6 months) History of stroke or transient ischemic attack (within last 6 months) Clinically significant peripheral vascular disease Evidence of bleeding diathesis or coagulopathy History of abdominal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess (within last 6 months) History of anaphylactic reaction to monoclonal antibody therapy not controlled with treatment premedication Serious non-healing wound, ulcer, or bone fracture. Fracture secondary to metastatic disease was allowed if stable and surgery (if applicable) was completed ≥28 days prior to study entry. General Exclusion Criteria Pregnancy or lactation Inadequate organ function, as evidenced by any of the following laboratory values: Absolute neutrophil count < 1500/µL Platelet count < 100,000/µL Total bilirubin > 1.5 mg/dL AST, and/or ALT > 2 x the upper limit of normal (> 5 x ULN in subjects with known liver involvement) Alkaline phosphatase > 2 ULN (> 5 x ULN in subjects with known liver involvement and > 7 > ULN in subjects with known bone involvement) Serum creatinine > 2.0 mg/dL PTT and/or either INR or PT > 1.5 x upper limit of normal (except for subjects receiving anti-coagulation therapy) Urine protein/creatinine ratio > 1.0 at screening for U.S. subjects, or urine dipstick for proteinuria ≥ 1+ at screening followed by 24-hour urine collection demonstrating > 1 g protein/24 hr for ex-U.S. subjects Uncontrolled serious medical or psychiatric illness Active infection requiring IV antibiotics at Day 0

	History of other malignancies within 5 years of Day 0 except for tumours with a negligible risk for metastasis or death, such as adequately controlled basal cell carcinoma or squamous-cell carcinoma of the skin or carcinoma in situ of the cervix Patients with a history of bilateral breast cancer or previous history of breast cancer were eligible.

The inclusion and exclusion criteria are consistent with the Summary of Product Characteristics for bevacizumab.

5.3.4 **Describe the patient characteristics at baseline. Highlight any differences between study groups.**

Table 5: Baseline Characteristics: Randomised Patients in the Capecitabine Cohort

	Cap + PL	Cap + BV	Total
	(n = 206)	(n = 409)	(n = 615)
Age (year)			
Median	57 (23−88)	56 (28−91)	56 (23−91)
Female	204 (99.0%)	408 (99.8%)	612 (99.5%)
Baseline ECOG performance status			
n	206	406	612
0	110 (53.4%)	214 (52.7%)	324 (52.9%)
1	96 (46.6%)	192 (47.3%)	288 (47.1%)
Number of metastatic sites			
< 3	113 (54.9%)	232 (56.7%)	345 (56.1%)
≥ 3	93 (45.1%)	177 (43.3%)	270 (43.9%)
Bone lesion only			
Yes	21 (10.2%)	36 (8.8%)	57 (9.3%)
No	185 (89.8%)	373 (91.2%)	558 (90.7%)
Hormone receptor status			
n	198	403	601
Positive (ER + and/or PgR +)	146 (73.7%)	312 (77.4%)	458 (76.2%)
Negative (ER − and PgR −)	52 (26.3%)	91 (22.6%)	143 (23.8%)
HER2 status by FISH/IHC			
n	202	400	602
Negative	196 (97.0%)	392 (98.0%)	588 (97.7%)
ER/PgR/HER2-ve (triple negative)			
N	198	401	599
Yes	50 (25.3%)	87 (21.7%)	137 (22.9%)
Disease-free interval (months)			
≤ 12	45 (21.8%)	109 (26.7%)	154 (25.0%)
> 12	161 (78.2%)	300 (73.3%)	461 (75.0%)
Measurable disease at baseline			
n	205	409	614
Yes	161 (78.5%)	325 (79.5%)	486 (79.2%)
No	44 (21.5%)	84 (20.5%)	128 (20.8%)
Prior treatment for primary breast cancer	190 (92.2%)	374 (91.4%)	564 (91.7%)
Surgery	188 (91.3%)	365 (89.2%)	553 (89.9%)
Chemotherapy	156 (75.7%)	288 (70.4%)	444 (72.2%)
Taxane	84 (40.8%)	161 (39.4%)	245 (39.8%)
Anthracycline-based agent	143 (69.4%)	247 (60.4%)	390 (63.4%)
Radiotherapy	140 (68.0%)	254 (62.1%)	394 (64.1%)

	Cap + PL	Cap + BV	Total
Hormonal therapy	109 (52.9%)	203 (49.6%)	312 (50.7%)
Prior treatment for locally recurrent or metastatic breast cancer	98 (47.6%)	207 (50.6%)	305 (49.6%)
Hormonal therapy	89 (43.2%)	188 (46.0%)	277 (45.0%)
Radiotherapy	49 (23.8%)	113 (27.6%)	162 (26.3%)

BV = bevacizumab; Cap = capecitabine; PL = placebo.

Note: Percentages are based on patients without missing information. ECOG = Eastern Cooperative Oncology Group; ER = oestrogen receptor, PgR = progesterone receptor, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor 2, IHC = immunohistochemistry

There are slightly fewer triple negative patients and slightly more hormone receptor positive patients in the capecitabine plus bevacizumab arm, this may be due to not stratifying for hormone receptor status. The numbers of patients who received a prior adjuvant taxane were similar between the two treatment arms.

Outcomes

5.3.5 **Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice).**

Primary endpoint

Progression free survival

The primary endpoint in the study was investigator assessed progression free survival (PFS) according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria (Therasse, P et al 2000). The RECIST criteria are the standard method of classifying tumour response to chemotherapy trials. PFS is a valid endpoint in this study as the effect of first line treatment can be accurately investigated. Patients had the option of receiving second line bevacizumab and chemotherapy, thus

establishing an overall survival benefit might be challenging due to confounding issues with cross-over.

PFS is defined as the time from randomisation to first disease progression or death due to any cause, whichever occurs first. Data for subjects without disease progression or death was censored at the time of the last tumor assessment (or, if no tumor assessments were performed after the baseline visit, at the time of randomisation plus 1 day).

The intent-to-treat (ITT) population is the primary analysis population for the primary endpoint. The ITT population consists of all subjects who are randomised, whether or not they receive any study drug or complete the full course of treatment.

Secondary endpoints

The secondary efficacy outcome measures in this study were as follows:

Objective response rate

Objective response is defined as a complete or partial response determined on two consecutive assessments ≥4 weeks apart. Objective response rate is the percentage of subjects who have objective response.

The primary analysis for objective response rate was performed using only subjects with measurable disease at baseline. The supportive analysis included the ITT population. Subjects without a post-baseline tumour assessment were considered non-responders.

Overall survival

Overall survival is defined as the time from randomisation until death from any cause. For subjects who had not died at the time of analysis or were lost to follow up, duration of survival was censored as of the date the subject was last known to be alive.

One-year survival rate

One-year survival rate is defined as the percentage of subjects who are still alive at one year after the randomisation.

Duration of objective response

For the subset of subjects who achieved objective responses during the treatment phase, duration of objective response was defined as the time from the first tumor

assessment that supports the subject's objective response to the time of disease progression, or death due to any cause, whichever occurs first. The censoring method for duration of objective response was the same as that for progression free survival.

PFS, based on IRC assessment

Disease progression was assessed by independent review committee (IRC) according to RECIST. PFS is defined as the time from randomisation to first disease progression, as determined by IRC, or death due to any cause, whichever occurs first. Data for subjects without IRC-determined disease progression or death were censored at the time of the last tumor assessment (or, if no tumor assessments were performed after the baseline visit, at the time of randomisation plus 1 day). Data for subjects who received excluded therapy prior to IRC-determined disease progression were also censored at the time of the last tumor assessment prior to the initiation of the excluded therapy.

PFS based on IRC-reviewed data was considered a secondary efficacy endpoint and served as a sensitivity analysis to support the investigator-determined assessment. Radiographic data were sent from investigative sites to the IRC.

Statistical analysis and definition of study groups

5.3.6 **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).**

Safety analyses

The following assumptions were made for the sample size calculation: two-sided log-rank test, 5% significance level, 2:1 randomisation ratio (treatment: placebo) and a projected enrolment to the capecitabine cohort of approximately 29 subjects per month.

A total of 600 subjects from the capecitabine cohort was planned to result in approximately 415 events during a total trial period of approximately 28 months; this

was planned to allow for approximately 80% power to detect an improvement in median time to disease progression or death from 6 months in the standard chemotherapy + placebo arm to 8 months in the chemotherapy + bevacizumab arm (HR = 0.75) at the 5% level of significance.

Analysis Populations

The primary efficacy analysis population was the intent-to-treat (ITT) population, defined as all subjects who were randomised, regardless of whether they received any study drug or complete the full course of treatment. A subject was considered to be randomly assigned to the treatment when the study site was notified of the subject's treatment arm assignment by the IVRS. Subjects were grouped according to the treatment assignment at randomisation.

The primary safety analyses were based on all randomised subjects who received any study treatment, defined as at least one full or partial dose of either study treatment or chemotherapy. This population was referred to as the safety population. Subjects were analysed as randomised. Subjects who received chemotherapy other than the cohort they were initially enrolled to were analysed based on their initial chemotherapy assignments for the safety analyses.

Primary Efficacy Analyses

Progression-Free Survival

Significance Level

The analysis of PFS was performed at the two-sided $\alpha = 0.05$ level.

Analysis Methods

PFS was formally tested using a two-sided stratified log-rank test.

The stratification factors were disease-free interval ($\leq$12 months, >12 months), prior adjuvant chemotherapy (yes, no) and number of metastatic sites (<3, $\geq$3) and capecitabine chemotherapy. Results from an unstratified log-rank test were also calculated. The Kaplan–Meier method (by therapy) was used to estimate median PFS for each treatment arm. The 95% confidence intervals for median PFS were computed using the Brookmeyer and Crowley method.

The null and alternative hypotheses regarding PFS analysis can be phrased in terms of the hazard ratio (HR), $\lambda A / \lambda B$, where λA and λB represent the hazard of progression in Arm A (capecitabine and bevacizumab) and Arm B (capecitabine and

placebo), respectively. The null and alternative hypotheses, respectively, can be written as follows:

$$H_0 : \frac{\lambda_A}{\lambda_B} = 1 \quad \text{versus} \quad H_a : \frac{\lambda_A}{\lambda_B} \neq 1$$

If the estimate of λ*A* / λ*B* <1 and results from the stratified log-rank test lead to the rejection of H_0 in favour of H_a in the capecitabine cohort, then it will be concluded that the combination of bevacizumab and capecitabine prolongs duration of PFS relative to capecitabine chemotherapy alone.

The hazard ratio, λ*A* /λ*B*, was estimated using a stratified Cox regression model with the same stratification variables used in the stratified log-rank test.

The unstratified hazard ratio was also calculated.

Secondary Efficacy Analyses

Secondary efficacy endpoints included objective response rate (ORR), overall survival (OS), one-year overall survival rate, duration of objective response, and PFS based on IRC-reviewed data.

For the key secondary endpoints of ORR, OS, and one-year survival rate the following test procedures were used to maintain a type I error rate of α=0.05 (two-sided).

Step 1: The secondary endpoint of ORR will be tested at the type I error rate of 0.01.

Step 2a: If a statistically significant result is observed in ORR, OS would be tested at the type I error rate of 0.05.

Step 2b: Otherwise, OS would be tested at the type I error rate of 0.04.

Step 3: One-year survival rate would be compared only when a statistically significant result is observed in OS between two treatment arms. The type I error rate for one year survival rate will be the same as that used for OS.

No adjustments for multiplicity (of endpoints or treatment comparisons) were incorporated into the analyses of duration of objective response and PFS based on IRC-reviewed data. The p-values from these analyses should be interpreted accordingly.

For all the stratified tests below, the stratification factors are disease-free interval (≥12 months, >12 months), prior adjuvant chemotherapy (yes, no), number of metastatic sites (<3, ≥3).

Objective Response Rate

ORR was formally compared between two treatment arms using the Mantel-Haenszel χ^2 test, stratified by the randomisation stratification factors. Fisher's exact test was also performed. An estimate of ORR and its 95% Blyth-Still-Casella exact confidence interval was calculated for each treatment arm. Confidence intervals for the difference in tumor response rate were also calculated.

One-Year Survival Rate

The Kaplan–Meier method was used to estimate one-year survival rate for each treatment arm, along with the 95% confidence intervals using Greenwood's formula. The difference in one-year survival rate between treatment arms was assessed using the normal approximation method.

The difference in one-year survival rate between two treatment arms was tested using a z-test.

Overall Survival

Approximately 295 deaths were expected in the capecitabine cohort, assuming a 3 month improvement in the median OS, from 24 months in the placebo arm to 27 months in the bevacizumab arm (HR = 0.89).

Stratified log-rank test was used to compare the duration of survival between treatment arms. The Kaplan–Meier method was used to estimate median OS for each treatment arm. Hazard ratio was estimated using the stratified Cox proportional hazards regression model.

Duration of Objective Response

Duration of objective response was estimated using the Kaplan-Meier method for each treatment arm. The 95% confidence intervals for median duration of objective response were computed using the Brookmeyer and Crowley method. Please note that the determination of duration of objective response was based on a non-randomised subset of subjects; no formal hypothesis testing was performed.

PFS Based on IRC-Reviewed Data

Analyses of PFS based on IRC-reviewed data were performed at the two-sided $\alpha = 0.05$. Stratified log-rank test was used to compare the duration of PFS between treatment arms. The Kaplan–Meier method was used to estimate median PFS for each treatment arm. Hazard ratio was estimated using the stratified Cox proportional hazards regression model. Unstratified log-rank test p-value and unstratified hazard ratio were also calculated.

Safety Analyses

Analysis of capecitabine exposure included total number of cycles or days on treatment and number of cycles or days of missed treatment for all subjects in the safety population.

Duration of follow-up for safety assessment during the blinded treatment phase was defined as the time from the first dose of study drug or chemotherapy to 30 days after the last dose of study drug or chemotherapy during the blinded treatment phase, or the start date of the open-label phase, whichever occurred first.

Adverse Events

The aim of the study was to evaluate toxicity as measured by the incidence of selected adverse events, adverse events resulting in treatment discontinuation, serious adverse events, and standard chemotherapy options with or without bevacizumab.

The protocol-defined selected adverse events are described as the following: Arterial thromboembolic events (Grade ≥ 2), Venous thromboembolic events (Grade ≥ 3), Hypertension (Grade ≥ 3), Gastrointestinal perforation (any grade), Bleeding (Grade ≥ 3), proteinuria (Grade ≥ 3), Sensory neuropathy (Grade ≥ 3), Wound dehiscence (Grade ≥ 3), Left ventricular systolic dysfunction (Grade ≥ 2), Neutropenia (Grade ≥ 3), Febrile neutropenia (Grade ≥ 3), Reversible posterior leukoencephalopathy syndrome (RPLS; any grade).

Verbatim descriptions of adverse events were mapped to MedDRA thesaurus terms and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0. All adverse events, serious adverse events, and adverse events leading to death and study treatment discontinuation were summarised by treatment arm and NCI-CTCAE grade. Adverse events were

also summarised by age, race, and geographic region. For events of varying severity, the highest grade was used in summaries.

Additionally, adverse events that occurred after disease progression but prior to the optional post-progression phase were summarised by the treatment group and chemotherapy regimen for the subset of subjects who continued on the blinded treatment phase after disease progression.

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Exploratory Efficacy Analyses

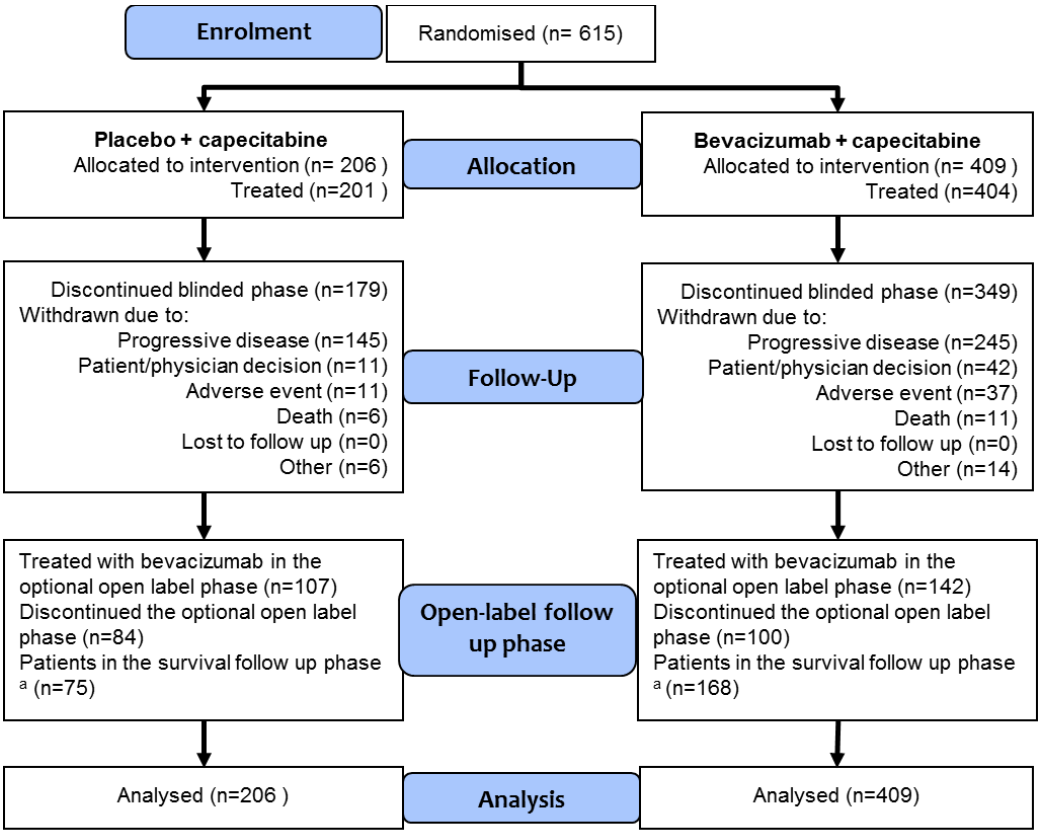
Subgroup Analyses

The heterogeneity in response to treatments for metastatic breast cancer varies considerably in the first line setting. Due to paucity of efficacy data in particular patient populations in great clinical need, the PFS and OS were calculated in a range of patient populations. The following variables were plotted on a forest plot (including estimated hazard ratios using unstratified Cox proportional hazards regression model) to assess the consistency of the treatment benefit: age, race, baseline ECOG performance status (0 vs. 1), menopausal status, number of metastatic sites, sites of involvement, disease measurability, SLD of target lesions, HR status, triple-negative status, disease-free interval, prior neoadjuvant/adjuvant chemotherapy, prior adjuvant hormone therapy, prior hormonal therapy for locally recurrent or metastatic disease, prior taxane therapy, prior anthracycline therapy and region. Although patients were stratified according to prior adjuvant treatment (yes or no), the specific type of adjuvant therapy (taxane or anthracycline) was not stratified.

Participant flow

5.3.8 **Provide details of the numbers of patients who were eligible to enter the RCT(s), 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 or withdrew from the RCT. This information should be presented as a CONSORT flow chart.**

Figure 3: CONSORT Flow Diagram – RIBBON-1



[a] = includes all patients who discontinued from either the blinded treatment phase or the optional open label post-progression phase

5.4 Critical appraisal of relevant RCTs

5.4.1 **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 that meets the criteria for inclusion should therefore be critically appraised.**

Please see Section 9.3, appendix 3

5.4.2 **Please provide as an appendix a complete quality assessment for each RCT.**

Please see Section 9.3, appendix 3.

5.5 Results of the relevant RCTs

5.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses. Information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.**

Please see results presented in section 5.5.2.

Data presented below is from the Xeloda and bevacizumab/placebo arm of the RIBBON-1 trial, as this data is from the licensed population of patients. At the time of data cutoff (31 July 2008 for main analysis), 291 PFS events (71.1%) in the Cap+BV arm and 162 PFS events (78.6%) in the Cap +PL arm had occurred. Median PFS was 8.6 and 5.7 months in the Cap+BV arm and Cap+PL arm, respectively. The stratified analysis of PFS showed that the addition of bevacizumab to capecitabine resulted in a statistically significant increase in PFS relative to the Cap+PL arm (HR = 0.69; 95% CI: 0.56-0.84; log-rank p= 0.0002). The results from the unstratified analysis of PFS were similar to those of the stratified analysis (HR =0.67; 95% CI: 0.55-0.82; log-rank p<0.0001). Table 6 shows the primary and secondary efficacy endpoints of the RIBBON-1 study.

Table 6: Overview of efficacy results for capecitabine cohort

Efficacy Parameter	Cap + PL (N = 206)	Cap + BV (N =409)
Primary Efficacy Parameter		
Progression–free survival (Investigator assessed)		
Number (%) of patients with an event	162 (78.6%)	291 (71.1%)
Median – months (95% CI)	5.7 (4.3-6.2)	8.6 (8.1–9.5)
Stratified analysis		
Hazard ratio (95% CI) a	0.69 (0.564; 0.840)	
p–value (log–rank)	0.0002	
Unstratified analysis		
Hazard ratio (95% CI) a	0.67 (0.55; 0.82)	
p–value (log–rank)	<0.0001	
Secondary Efficacy Parameters		
Number of patients with measurable disease	161	325
Objective response b	38 (23.6%)	115 (35.4%)
p–value (stratified analysis)	0.0097	
Between–arm difference (95% CI)	11.8% (3.4%; 20.2%)	
Complete response	1 (0.6%)	7 (2.2%)
Partial response	37 (23.0%)	108 (33.2%)
Duration of objective response		
Patients with objective response	38	115
Patients with an event (%)	26 (68.4%)	70 (60.9%)
Median - months (95% CI)	7.2 (5.1; 9.3)	9.2 (8.5; 10.4)
Number of patients who died (updated analysis)	99 (48.1%)	186 (45.4%)
Overall survival (stratified analysis)		
Median – months (95% CI)	22.8 (20.5-28.4)	25.7 (22.0-28.4)
Hazard ratio (95% CI) a	0.88 (0.69; 1.13)	
p–value (log–rank)	0.33	
One–year survival rate (updated analysis)		
Survival rate	74.8%	81.0%
Difference in one–year survival rate (95% CI) c	6.2% (-1.0%; 13.4%)	
p–value	0.092	
Progression–free survival (IRC assessed – stratified analysis)		
Number (%) of patients with an event	119 (57.8%)	219 (53.5%)
Median –months (95%CI)	6.2 (4.7-7.8)	9.8 (8.4-10.4)
Hazard ratio (95% CI) a	0.68 (0.54; 0.86)	
p–value (log–rank)	0.0011	
Key Sensitivity Analysis		
Progression–free survival (Investigator assessed, not censored for NPT - stratified analysis)		
Number (%) of patients with an event	168 (81.6%)	309 (75.6%)
Median -months)	5.5	8.8

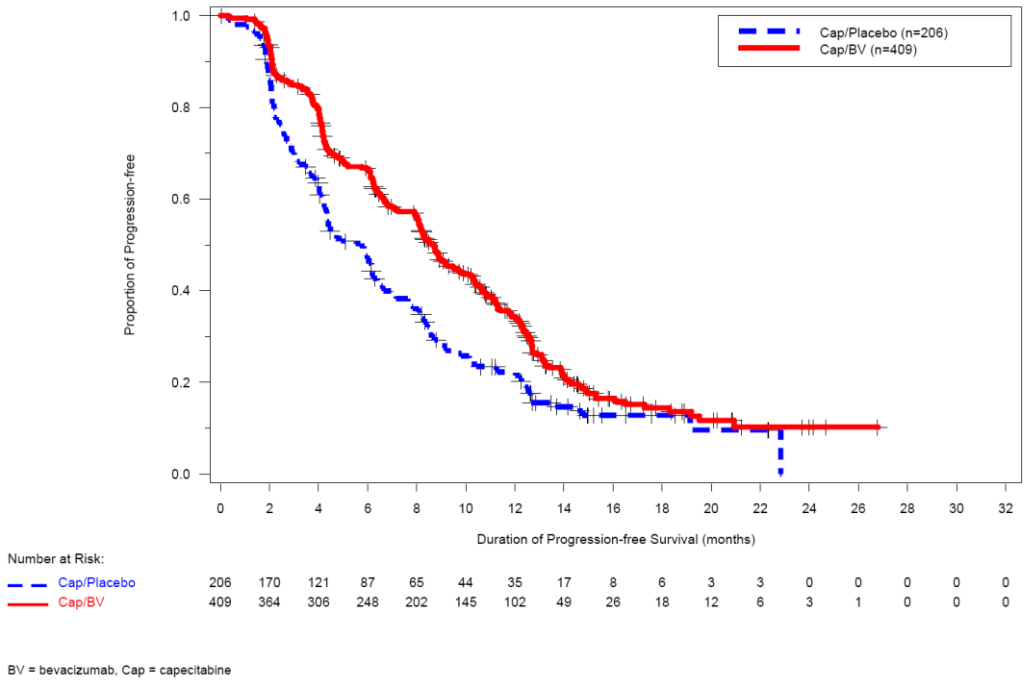
Efficacy Parameter	Cap + PL (N = 206)	Cap + BV (N =409)
Hazard ratio (95% CI) a	0.66 (0.55; 0.81)	
p–value (log–rank)	< 0.0001	
BV = bevacizumab; Cap = capecitabine; CI = confidence interval; IRC = Independent Review Committee; NPT = non-protocol specified antineoplastic therapy; Pl = placebo; Clinical data cut-off original analysis: July 31, 2008; updated analysis: February 23, 2009; a Relative to placebo b partial or complete response confirmed c Clinical data cut-off original analysis: July 31, 2008; updated analysis: February 23, 2009		

PROGRESSION FREE SURVIVAL

Progression Free Survival: Investigator Assessed (Primary efficacy endpoint)

The addition of bevacizumab to capecitabine as first-line therapy for locally recurrent or metastatic breast cancer resulted in a clinically meaningful and statistically significant improvement in PFS compared to capecitabine alone (stratified analysis: HR = 0.69; log-rank p = 0.0002). The median PFS was 8.6 months in the Cap-BV arm and 5.7 months in the Cap-PL arm. The PFS curve separates early, showing that even poor prognosis patients obtain benefit (Figure 4).

Figure 4: Kaplan-Meier plot of PFS (investigator assessed) in the capecitabine cohort (ITT population) censored for NPT

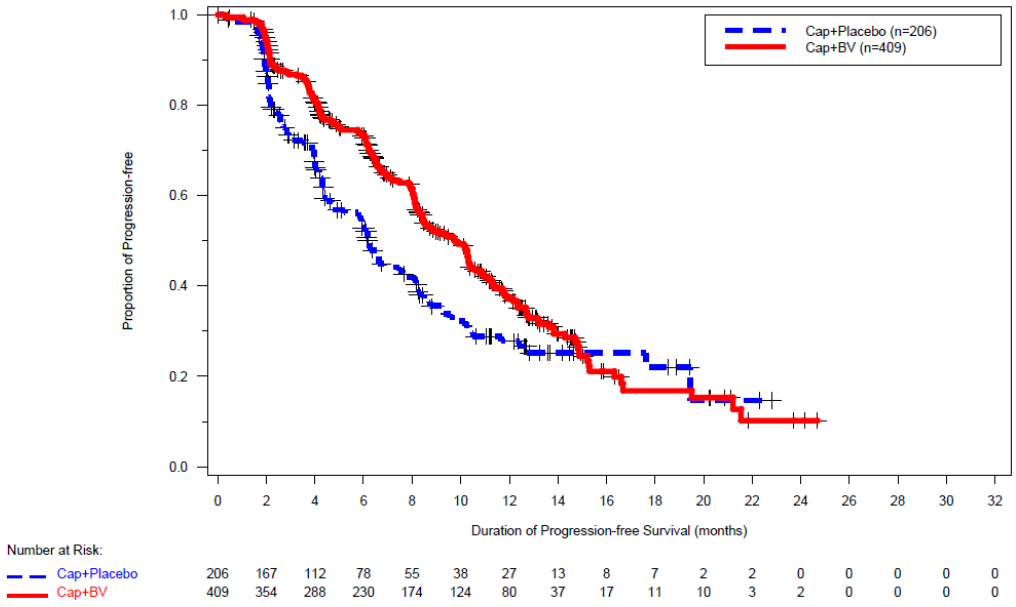


BV = bevacizumab, Cap = capecitabine

Progression-free Survival: IRC-assessed

Median PFS based on the IRC assessment was 9.8 months in the Cap+BV arm vs. 6.2 months the Cap+PL arm. A significant improvement of 3.6 months arose with Cap+BV vs Cap+PL (stratified analysis HR = 0.68, 95% CI: 0.54- 0.86, p-value log-rank= 0.0011) (Figure 5).

Figure 5: Kaplan-Meier plot of PFS (IRC-assessed) in the capecitabine cohort (ITT population)



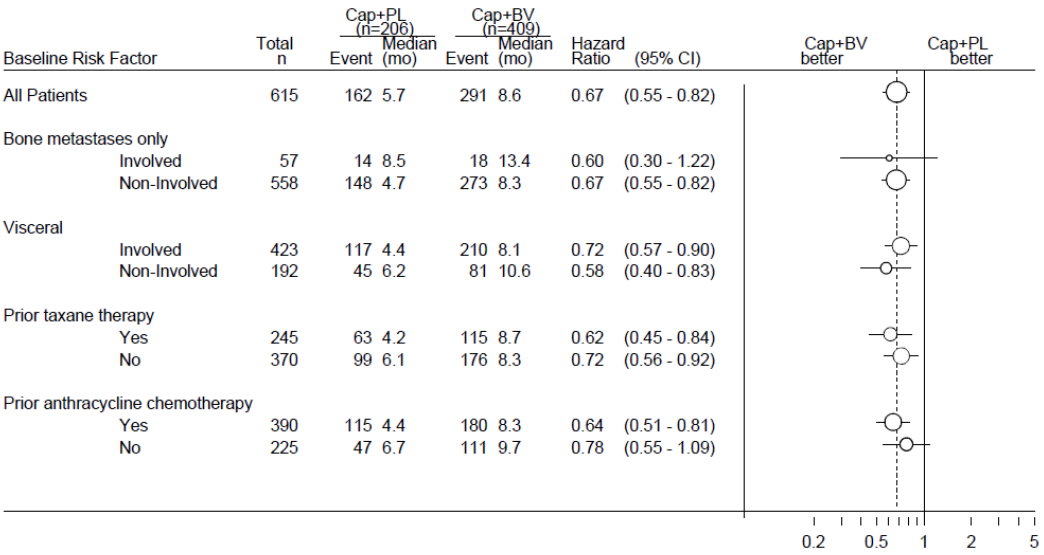
Progression Free Survival: subgroup data

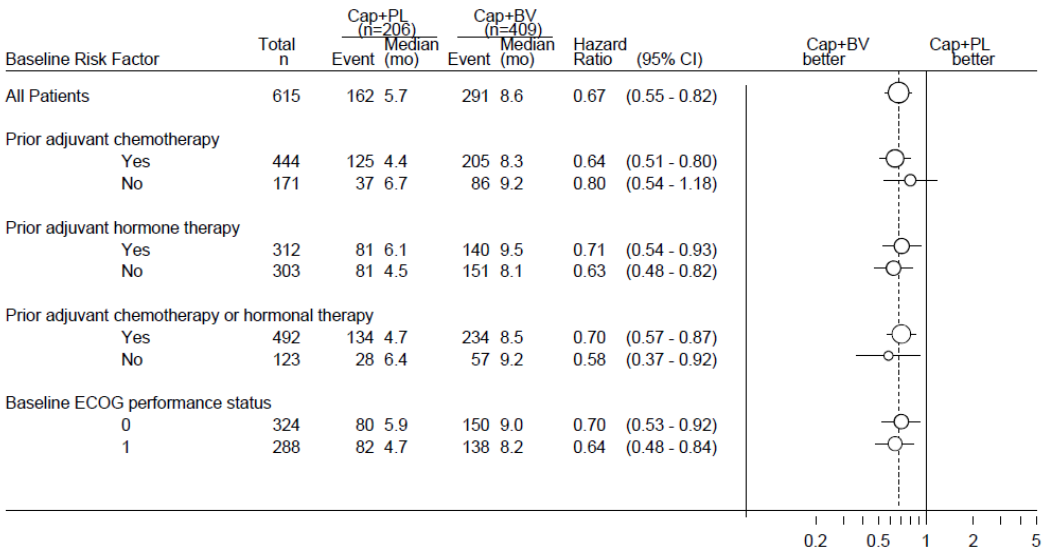
A PFS benefit of bevacizumab vs placebo with capecitabine was observed in pre-specified subgroups defined by stratification variables (disease-free interval, number of metastatic sites, prior adjuvant chemotherapy), age, race, baseline ECOG performance status, sites of involvement, disease measurability, SLD of target lesions at baseline, estrogen receptor status, hormone receptor status, triple-negative status, prior adjuvant hormone therapy, prior hormonal therapy for locally recurrent or metastatic disease, prior taxane therapy, and prior anthracycline therapy (Figure 6).

As defined in the decision problem, patients who have received prior taxane and anthracycline regimens have few treatment options and are the patient group eligible for monotherapy with capecitabine, within its licensed indication. Subgroup analysis

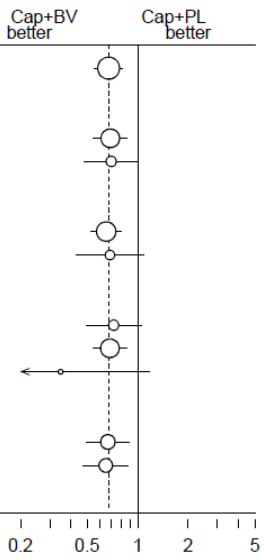
of patients who have had a prior adjuvant or neoadjuvant taxane demonstrated that the median PFS more than doubled from 4.2 months with Cap+PL to 8.7 months with Cap+BV (HR= 0.62, 95% CI: 0.45-0.84) (n=245). These prior taxane treated patients in the Cap-PL arm do considerably worse than the patients in the ITT analysis; the addition of bevacizumab to capecitabine raises their PFS to a level similar to the ITT population.

Figure 6: Progression-Free Survival by Baseline Risk Factor for Patients in the Capecitabine Cohort Randomised Patients

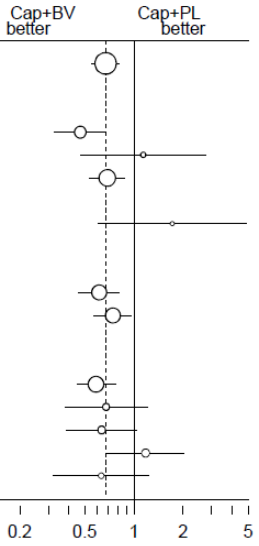




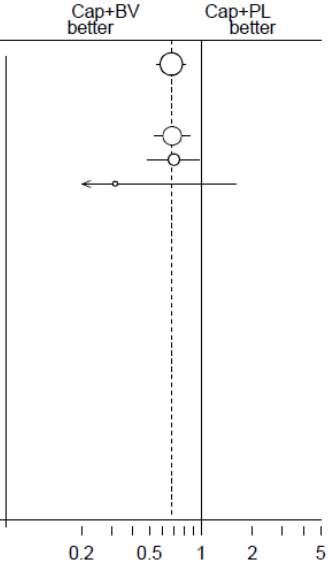
Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	162	5.7	291	8.6	0.67	(0.55 - 0.82)
Hormone receptor status							
Positive	458	110	6.2	211	9.2	0.69	(0.55 - 0.87)
Negative	143	44	4.2	77	6.1	0.70	(0.48 - 1.01)
Disease measurability							
Yes	486	133	4.4	245	8.2	0.65	(0.53 - 0.80)
No	128	29	7.8	46	12.3	0.68	(0.43 - 1.09)
ER/PgR/HER2- triple negative							
Yes	137	42	4.2	74	6.1	0.72	(0.49 - 1.06)
No	462	112	6.1	213	9.2	0.68	(0.54 - 0.86)
Unknown	16	8	3.9	4	12.4	0.35	(0.10 - 1.18)
Baseline SLD of target lesions (cm)							
< Median (6.50)	262	73	4.4	133	8.0	0.67	(0.50 - 0.89)
>= Median	239	63	4.4	121	8.2	0.65	(0.47 - 0.88)



Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	162	5.7	291	8.6	0.67	(0.55 - 0.82)
Menopausal status							
Premenopausal	180	49	4.4	85	8.9	0.47	(0.33 - 0.68)
Perimenopausal	37	7	9.5	17	6.5	1.14	(0.47 - 2.76)
Postmenopausal	370	101	4.7	175	8.5	0.69	(0.54 - 0.88)
Not Applicable	2	0	.	1	12.4		(-)
Unknown	26	5	9.8	13	8.8	1.72	(0.60 - 4.87)
Region							
US	309	72	4.4	147	8.9	0.61	(0.46 - 0.81)
Ex-US	306	90	6.1	144	8.1	0.74	(0.57 - 0.97)
Region							
North America	330	81	4.4	158	8.9	0.59	(0.45 - 0.77)
Latin America	66	19	5.1	31	8.1	0.68	(0.38 - 1.21)
Eastern Europe	85	28	6.1	38	8.5	0.63	(0.39 - 1.04)
Western Europe	85	19	8.6	42	7.1	1.18	(0.69 - 2.04)
Asia	49	15	6.7	22	8.1	0.63	(0.32 - 1.23)



Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	162	5.7	291	8.6	0.67	(0.55 - 0.82)
ER status							
Positive	440	106	6.2	201	9.5	0.68	(0.54 - 0.86)
Negative	164	50	4.0	88	5.2	0.69	(0.49 - 0.99)
Unknown	11	6	4.9	2	12.4	0.32	(0.06 - 1.60)



BV = bevacizumab; Cap = capecitabine; CI = confidence interval; PL = placebo; SLD = sum of longest diameters; US = United States. Hazard ratio relative to placebo was estimated by unstratified Cox regression model. Median duration of progression-free survival was estimated from Kaplan-Meier curves.

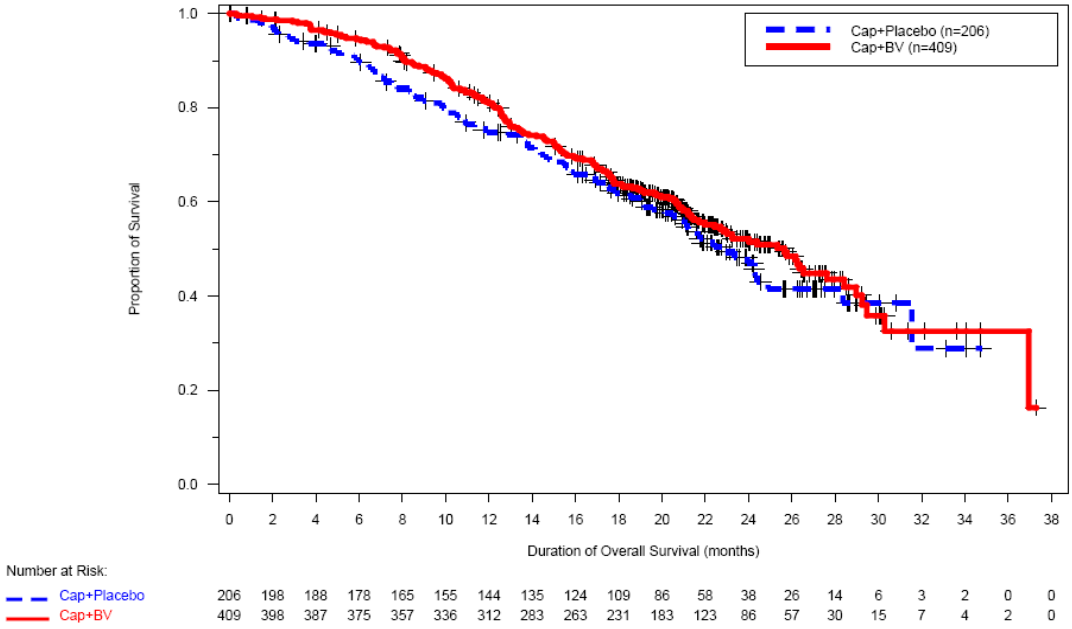
OVERALL SURVIVAL

Overall Survival – ITT population

The overall survival data and one-year survival rate data are based on updated analyses and include the open label phase of the study. The data cut off for these analyses was 28th February 2009. As previously discussed the trial was not powered to show differences in overall survival. In the ITT population the median overall survival was 25.7 months in the Cap + BV arm and 22.8 months in the Cap + PL arm. The Kaplan Meier plot of OS is presented in Figure 7 and demonstrates that patients in the Cap+BV arm had a 2.9 month improvement in median OS; however, this did not translate into a statistically significant improvement (stratified HR = 0.88, 95% CI: 0.69-1.12, p = 0.33).

Various sensitivity analyses of overall survival yielded results that were similar to those based on the main analysis. The estimated hazard ratio for overall survival, based on the stratified analysis was 0.85 (95% CI: 0.63, 1.14; p = 0.27). However, two thirds of patients received bevacizumab in the open label post progression phase; this amount of cross over to bevacizumab in the open label phase of the study may confound the OS results, as the study was not designed to evaluate the effect of subsequent therapies.

Figure 7: Kaplan Meier Plot of OS (Investigator Assessed) Capecitabine Cohort (ITT Population – Updated Analysis)

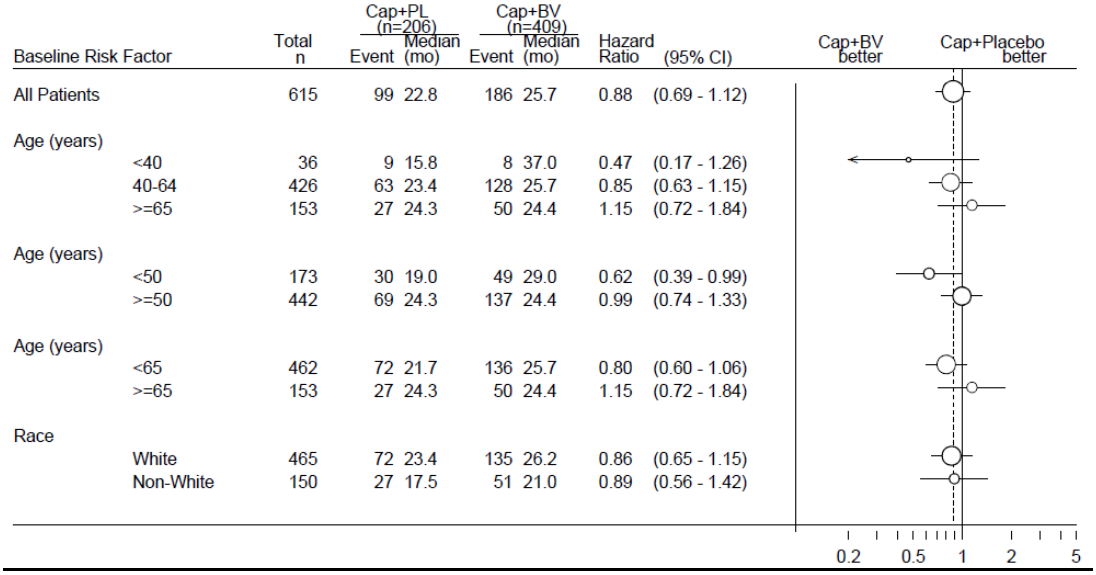


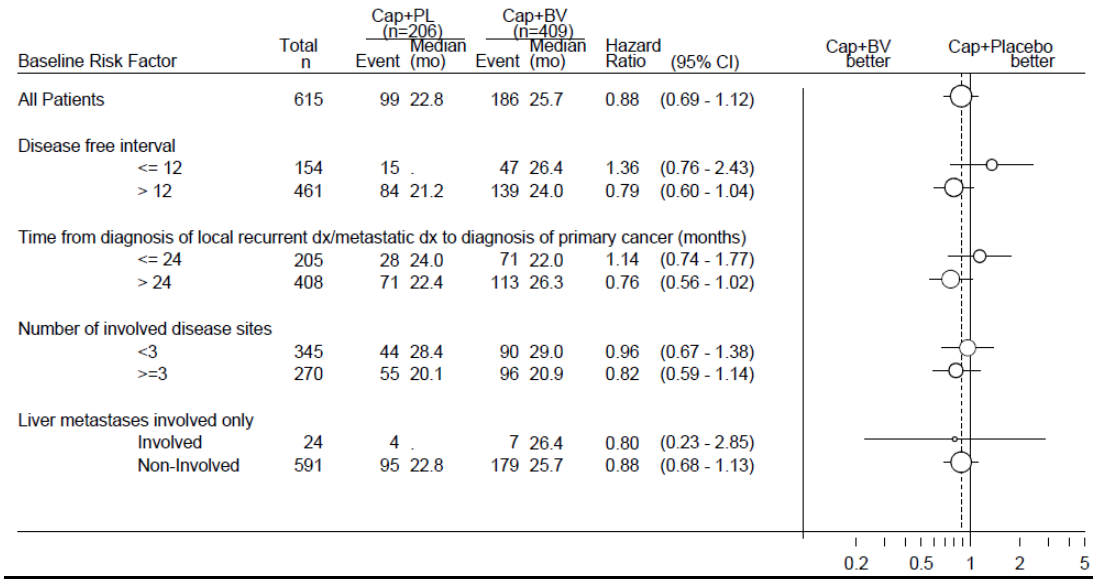
Although an overall survival difference was not apparent in the ITT population, it is evident from the separation of the KM curves (Figure 7) in the first year that some poor prognosis patients may have an OS benefit from Cap+BV treatment. Patients in the first year of treatment are less likely to crossover to receive bevacizumab in the open label phase of the study because of their limited time to receive subsequent therapy.

Overall Survival: Subgroup data

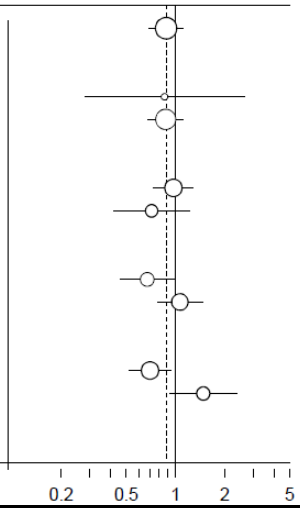
Forest plots of overall survival for baseline risk demonstrate that some subgroups derived a greater overall survival benefit than the ITT population (e.g prior taxane and anthracycline chemotherapy). Figure 8 demonstrates subgroup analysis of OS for patients in the RIBBON-1 study.

Figure 8: Overall Survival by Baseline Risk Factor for Patients in the Capecitabine Cohort Randomised Patients

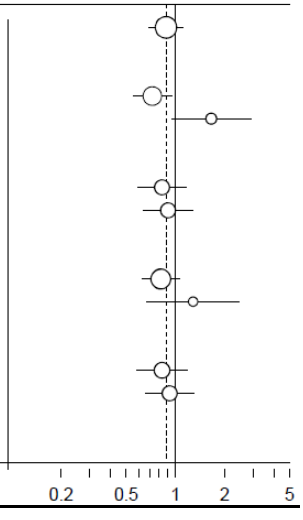




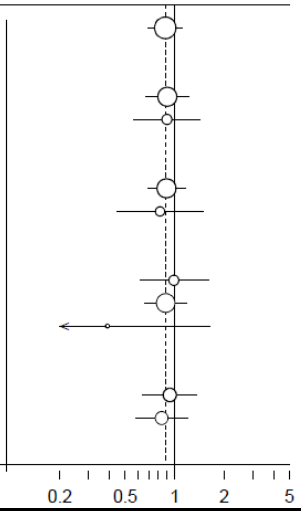
Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	99	22.8	186	25.7	0.88	(0.69 - 1.12)
Bone metastases only							
Involved	57	5	.	8	.	0.86	(0.28 - 2.64)
Non-Involved	558	94	21.9	178	23.3	0.87	(0.68 - 1.12)
Visceral							
Involved	423	78	21.2	149	21.3	0.97	(0.74 - 1.28)
Non-Involved	192	21	31.5	37	.	0.72	(0.42 - 1.23)
Prior taxane therapy							
Yes	245	44	20.5	70	28.4	0.67	(0.46 - 0.98)
No	370	55	24.3	116	24.4	1.07	(0.77 - 1.47)
Prior anthracycline chemotherapy							
Yes	390	76	20.5	108	25.7	0.70	(0.52 - 0.94)
No	225	23	28.4	78	25.3	1.49	(0.93 - 2.37)

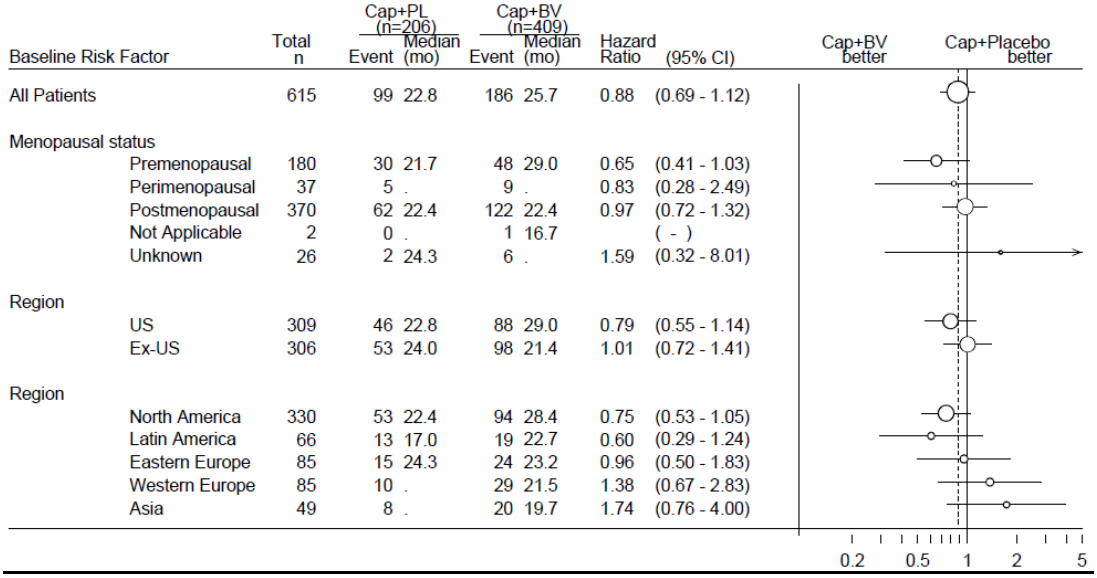


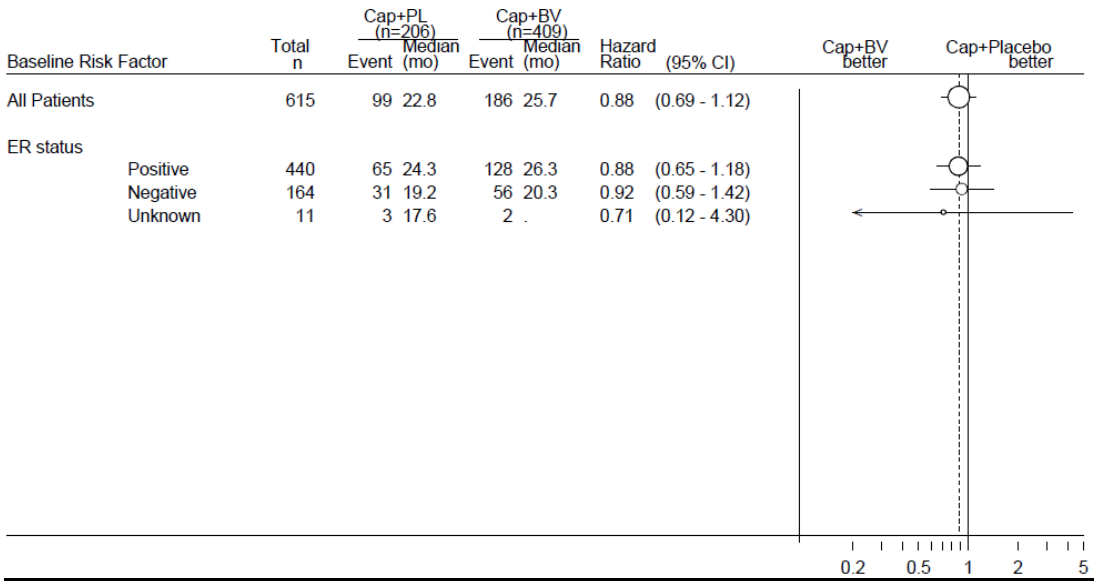
Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	99	22.8	186	25.7	0.88	(0.69 - 1.12)
Prior neo-adjuvant/adjuvant chemotherapy							
Yes	444	83	20.5	128	25.7	0.73	(0.55 - 0.96)
No	171	16	31.5	58	25.8	1.66	(0.95 - 2.89)
Prior adjuvant hormone therapy							
Yes	312	52	23.4	88	25.8	0.83	(0.59 - 1.17)
No	303	47	22.8	98	23.2	0.90	(0.64 - 1.28)
Prior adjuvant chemotherapy or hormonal therapy							
Yes	492	87	21.2	148	25.3	0.82	(0.63 - 1.07)
No	123	12	.	38	26.4	1.28	(0.67 - 2.46)
Baseline ECOG performance status							
0	324	49	23.4	87	27.6	0.83	(0.59 - 1.18)
1	288	50	22.4	98	22.4	0.93	(0.66 - 1.30)



Baseline Risk Factor	Total n	Cap+PL (n=206) Event	Cap+PL (n=206) Median (mo)	Cap+BV (n=409) Event	Cap+BV (n=409) Median (mo)	Hazard Ratio	(95% CI)
All Patients	615	99	22.8	186	25.7	0.88	(0.69 - 1.12)
HR status							
Positive	458	66	24.3	135	26.3	0.91	(0.67 - 1.22)
Negative	143	28	19.2	48	19.9	0.90	(0.56 - 1.43)
Disease measurability							
Yes	486	82	21.2	157	23.0	0.89	(0.68 - 1.17)
No	128	17	31.5	29	30.3	0.82	(0.45 - 1.49)
ER/PR/HER2- triple negative							
Yes	137	26	20.5	47	19.7	0.99	(0.61 - 1.60)
No	462	68	24.3	136	26.3	0.88	(0.66 - 1.18)
Unknown	16	5	10.6	3	.	0.39	(0.09 - 1.65)
Baseline SLD of target lesions (cm)							
< Median (6.50)	262	39	24.3	80	25.8	0.93	(0.64 - 1.37)
>= Median	239	45	19.6	83	21.5	0.83	(0.58 - 1.20)







The 4.5 month PFS benefit observed in patients who had a previous adjuvant taxane and received bevacizumab and capecitabine was conveyed into an OS benefit. Patients who had a prior adjuvant taxane had a median overall survival benefit of 7.9 months when receiving Cap+Bev compared to Cap+PL (HR = 0.67, 95%CI: 0.46-0.98). The OS increased from 20.5 months in patients who had received Cap+PL to 28.4 months with Cap+Bev suggesting statistical significance. The poor OS such patients have with capecitabine is raised above the level (25.7 months) found in the ITT population with capecitabine plus bevacizumab.

One-year Survival Rate – ITT population

A statistically significant difference in the 1-year survival rate was not detected between the two treatment arms. The one-year survival rate was 81.0% in the Cap+BV arm vs. 74.8%, in the Cap+PL arm ($p = 0.092$) in the updated analysis.

Objective Response Rate – ITT population

After adjusting for multiple comparisons of secondary endpoints, the addition of bevacizumab to capecitabine resulted in a clinically meaningful and statistically significant improvement in objective response rate: 35.4% in the Cap+Bev arm and 23.6% in the Cap-PL arm (p = 0.0097). The median duration of objective response was 9.2 months in the Cap+BV arm (9.2 months) vs. 7.2 months in the Cap+PL arm.

5.6 Meta-analysis

As only one RCT (RIBBON-1) was considered appropriate for inclusion with respect to the decision problem, no meta-analysis was conducted.

5.7 Indirect and mixed treatment comparisons

An indirect comparison of bevacizumab in combination with capecitabine compared with vinorelbine was not necessary in this setting given the findings of the recent clinical guideline, NICE CG81 which assumed no significant difference in survival outcomes for vinorelbine compared to capecitabine based on a single under-powered study in women who had been heavily pre-treated (NICE CG81 2009;Pajk et al. 2008).

5.8 Non-RCT evidence

Non-RCTs were not assessed

5.9 Adverse events

5.9.1 **If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results.**

Safety was a secondary endpoint in the RIBBON-1 study, not a primary endpoint therefore no searches were undertaken for this purpose.

5.9.2 **Please provide details of all important adverse events for each intervention group. For each group, give the number with the**

adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

RIBBON-1

Adverse events reported in this study were summarised by treatment arm and chemotherapy class (Table 7). As the safety profile of bevacizumab is well-characterised, this study focused on the collection of adverse events thought to be relevant to bevacizumab. In particular, these included ATE events (Grade ≥2), VTE events (Grade ≥3), hypertension (Grade ≥3), GI perforation (any grade), bleeding (Grade ≥3), proteinuria (Grade ≥3), sensory neuropathy (Grade ≥3), wound dehiscence (Grade ≥3), left ventricular systolic dysfunction (Grade ≥2), neutropenia (Grade≥3), febrile neutropenia (Grade ≥3), and RPLS.

Overall, no new safety signals were noted with the addition of bevacizumab to chemotherapy relative to events identified in the bevacizumab prescribing information.

The incidence of adverse events was higher in the bevacizumab-containing arm than in the placebo-containing arm. It is worth noting that the duration of treatment in the bevacizumab containing arm was greater than that in the placebo containing arm and the number of adverse events has not been adjusted for duration of therapy. The magnitude of the increase in incidence of selected adverse events between treatment arms was consistent with that described in the bevacizumab prescribing information.

The incidence of serious adverse events was higher in the bevacizumab-containing arm than in the placebo-containing arm, there were not serious adverse events which occurred in the bevacizumab containing arm that occurred at a frequency of more than 2% above the placebo arm. The overall death rate and the rate of deaths due to reasons other than disease progression were comparable between treatment arms.

The safety data presented is an overview during the blinded phase and is based on the later clinical cut-off date of 23 February 2009. 184 patients in the Cap + BV arm and 120 patients in the Cap + PL arm received treatment in the open label post progression phase.

Table 7: Overview of Safety During the Blinded Study Treatment Phase (safety population)

Parameter	Cap + PL (n = 201)	Cap + BV (n = 404)
No. (%) patients with at least one:		
Adverse event [a]	54 (26.9%)	162 (40.1%)
Grade 3–5 adverse event	46 (22.9%)	148 (36.6%)
Serious adverse event	41 (20.4%)	102 (25.2%)
Adverse event leading to bevacizumab or placebo discontinuation	24 (11.9%)	51 (12.6%)
Adverse event of special interest	18 (9.0%)	92 (22.8%)
All deaths (including disease progression)	97 (48.3%)	185 (45.8%)
Deaths unrelated to disease progression [b]	5 (2.5%)	6 (1.5%)
AEs leading to death	7 (3.5%)	10 (2.5%)
No. (%) patients with at least one [c]:		
Arterial thromboembolic event	3 (1.5%)	8 (2.0%)
Bleeding	1 (0.5%)	1 (0.2%)
Fistula	1 (0.5%)	1 (0.2%)
Hypertension	2 (1.0%)	43 (10.6%)
Left ventricular systolic dysfunction	1 (0.5%)	6 (1.5%)
Neutropenia	2 (1.0%)	5 (1.2%)
Proteinuria	0 (0.0%)	9 (2.2%)
Sensory neuropathy	1 (0.5%)	12 (3.0%)
Venous thromboembolic event	7 (3.5%)	20 (5.0%)
Wound dehiscence	0 (0.0%)	3 (0.7%)

BV = bevacizumab; Cap = capecitabine; Pl = placebo; * compared to placebo, CI not available. a Adverse events collected as per study protocol (adverse events of special interest, adverse events resulting in treatment discontinuation, serious adverse events,) b Deaths occurring within 30 days of the last dose of study drug due to a reason other than disease progression. c Adverse events of special interest identified through clinical review. GI perforations, febrile neutropenia and RPLS were not observed in any patients in the Cap-BEV or Cap-PL arm.

Safety summary – open label phase

Analyses of selected adverse events, serious adverse events, adverse events leading to study drug discontinuation, and deaths in the open label post progression phase show little change with respect to the incidence or severity of adverse events from the results previously reported in the blinded treatment phase.

No new safety signals were observed in the open-label phase with the use of bevacizumab in pre-treated patients with MBC. The safety profile was consistent with that observed in other bevacizumab studies.

The addition of bevacizumab to chemotherapy resulted in adverse events that were predictable, based on previous bevacizumab experience, and manageable and, with

the exception of hypertension, occurred at a low incidence (10.6% in the Cap + BV arm vs. 1.0% in the Cap + PL arm).

The addition of bevacizumab to chemotherapy regimens did not lead to a clinically relevant increase in adverse events that were typically associated with chemotherapy doublet regimens, such as febrile neutropenia, neutropenia, and sensory neuropathy.

The incidence of adverse events leading to study drug (Bev/PL) discontinuation was comparable across the two treatment arms of the capecitabine cohort (12.6% in the Cap +BV arm vs. 11.9% in the Cap +PL arm).

The incidence of deaths unrelated to disease progression, defined as deaths occurring within 30 days of the last dose of study drug due to a reason other than disease progression, was similar across treatment arms - 1.5% in the Cap + BV arm vs. 2.5% in the Cap + PL arm. The incidence of adverse events in the open-label phase was similar to that in the blinded treatment phase. The incidence of Grade 5 adverse events in the open-label phase was lower than that in the blinded treatment phase.

5.9.3 **Give a brief overview of the safety of the technology in relation to the decision problem.**

Overall, no new safety signals were noted with the addition of bevacizumab to chemotherapy relative to events identified in the bevacizumab prescribing information. The addition of bevacizumab to capecitabine resulted in adverse events that were predictable, based on previous bevacizumab experience, and generally manageable.

5.10 Interpretation of clinical evidence

5.10.1 **Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.**

In the RIBBON-1 trial, the addition of bevacizumab to capecitabine as first-line therapy for locally recurrent or metastatic breast cancer resulted in a clinically meaningful and statistically significant improvement in PFS in the ITT population (stratified analysis: HR = 0.69; log-rank p = 0.0002). The hazard ratio of 0.69 represents a 31% reduction in the relative risk of disease progression. This

progression free survival benefit was supported by the IRC assessed results (HR = 0.68, p = 0.0011).

A PFS benefit from bevacizumab was observed in all pre-specified subgroups. As outlined in the Context section above, patients who have relapsed with metastatic disease after receiving both an anthracycline and a taxane (≈ prior taxane treated patients in RIBBON-1) in the adjuvant setting have limited treatment options. They represent a great unmet clinical need, having received and failed two of the most effective treatments. These are a group of patients covered by the licensed indication for Xeloda (capecitabine); other patients from the RIBBON-1 study are not all covered by the current Xeloda licence and so cannot be considered for NHS reimbursement. Results from the RIBBON-1 trial highlighted that this large subgroup of patients (n=245) had a median PFS extension of 4.5 months with capecitabine and bevacizumab compared to capecitabine and placebo (HR= 0.62, 95% CI: 0.45-0.84). The hazard ratio of 0.62 represents a 38% in relative risk of disease progression.

The PFS benefit observed in this subgroup conveyed to an overall survival benefit, although the trial was neither powered, nor designed to detect a difference in overall survival. A significant increase in overall survival of 7.9 months was observed in patients in this subgroup who received bevacizumab and capecitabine compared to capecitabine and placebo (HR = 0.67, 95%CI: 0.46-0.98). This increase in overall survival meant that among patients given prior taxane therapy (who had a worse outcome with capecitabine and placebo than the ITT population), overall survival was increased to the level seen in the ITT population when given bevacizumab. The increase in overall survival is particularly powerful, as it is likely to have been compromised by patients who crossed over to receive second line bevacizumab in the open label phase of the trial. In total, two thirds of patients in the capecitabine-placebo arm crossed over to receive bevacizumab in subsequent lines of therapy.

Although a numerical advantage in overall survival and the 1-year survival rate was observed in the ITT population of patients treated with bevacizumab and capecitabine compared to capecitabine and placebo alone, the difference was not statistically significant. The estimated hazard ratio for overall survival, based on the stratified analysis, was 0.88 (95% CI: 0.69-1.13, p = 0.33). The 1-year survival rate was 81.0% in the bevacizumab-containing arm and 74.8% in the placebo-containing arm (p = 0.092). This equates to an 8.3% relative increase in 1-year survival rate in the bevacizumab arm.

After adjusting for multiple comparisons of secondary endpoints, the addition of bevacizumab to capecitabine also resulted in a clinically meaningful and statistically significant improvement in the ITT population objective response rate: 35.4% in the bevacizumab-containing arm and 23.6% in the placebo-containing arm (p = 0.0097).

Safety Conclusions:

Overall, no new safety signals were noted with the addition of bevacizumab to chemotherapy relative to events identified in the bevacizumab prescribing information. The addition of bevacizumab to capecitabine resulted in adverse events that were predictable, based on previous bevacizumab experience, and generally manageable. Adverse events occurred at a low incidence, with the exception of grade 3/4 hypertension, which arose at 10.1% in the capecitabine and bevacizumab arm vs. 1.0% in the capecitabine and placebo arm. The magnitude of the difference in the incidence of bevacizumab-related adverse events between bevacizumab-containing and placebo-containing arms was consistent with that reported in previous bevacizumab studies.

The duration of chemotherapy was longer in the capecitabine and bevacizumab arm than in the placebo arm. More than 30% of patients received at least 12 cycles of therapy. There was no adjustment for differences in treatment duration when comparing the relative toxicities in each treatment arm. The addition of bevacizumab to capecitabine did not lead to a clinically relevant increase in adverse events that were typically associated with chemotherapy regimens, such as febrile neutropenia, neutropenia, and sensory neuropathy.

The incidence of adverse events leading to study drug discontinuation was comparable between treatment arms (12.6% in the capecitabine and bevacizumab arm vs. 11.9% in the capecitabine and placebo arm).The incidence of deaths unrelated to disease progression was 1.5% in the bevacizumab and capecitabine arm vs. 2.5% in the capecitabine and placebo arm.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths:

The RIBBON-1 study is a double-blind, randomised, controlled trial that was conducted in multiple centres in Europe and the US. 615 patients were recruited into the capecitabine cohort of the study.

Efficacy analysis of pre-specified subgroups allowed data collection from patient populations who currently have an unmet clinical need and require new treatment options.

Limitations:

Investigators were able to choose the chemotherapy partner (between capecitabine and taxane/anthracycline) in a non-randomised way, hence there may be bias toward the patient-type selected to receive capecitabine chemotherapy. However, this most probably reflects the clinicians' treatment decision in routine clinical practice.

The trial design entitled patients in the capecitabine and placebo arm to receive bevacizumab in the second line open-label phase of the study; two thirds of patients in this arm consequently received bevacizumab in this setting, which is likely to have confounded overall survival results.

5.10.3 Please 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.

Relevance of evidence to the decision problem

The evidence base is directly relevant to the decision problem. The decision problem in this submission highlights the lack of NICE recommendations for and the challenge of treating mBC patients who have received a previous taxane and anthracycline in the adjuvant setting. The clinical evidence highlighted in section 5 demonstrates that poor prognosis patients (including those who have received a prior taxane) would benefit from the doublet combination of bevacizumab and capecitabine.

The following section highlights guidelines and clinical evidence for using capecitabine and bevacizumab in patients who are not eligible for taxane therapy.

Rationale for using capecitabine in first line metastatic patients

A challenge facing many UK oncologists is the increasing number of patients who have been exposed to taxanes and anthracyclines in the adjuvant setting. There are currently no specific recommendations for therapy in patients who have been treated with an anthracycline and a taxane in the adjuvant setting and who have progressed to metastatic disease.

The NICE Clinical Guideline 81 recommends the use of anthracycline where appropriate, or docetaxel in the first line setting, and capecitabine or vinorelbine as second or subsequent line therapies in metastatic breast cancer (NICE CG81 2009). When patients present with metastatic breast cancer with aggressive disease many will have already received docetaxel in the adjuvant setting, and clinicians may have to use perceivably less efficacious monotherapy treatments such as capecitabine and vinorelbine. Clinicians have an additional option to re-challenge with a taxane upon progression to metastatic disease, though they are often unwilling to re-treat these patients in light of potential taxane resistance, or if the patient experienced previous taxane toxicity.

Capecitabine therapy is an integral part of the treatment pathway of patients who have previously received a taxane. Capecitabine monotherapy is licensed for the treatment of metastatic breast cancer after failure of taxanes and an anthracycline-containing chemotherapy regimen (Xeloda SPC 2011). The use of capecitabine in this patient population is therefore a validated and licensed treatment option.

In the UK, capecitabine is the most widely used monotherapy treatment in patients who are unsuitable for a taxane (Data on File 2011). UK market research shows that approximately 50% of patients who receive a taxane and anthracycline in the adjuvant setting in the UK will receive capecitabine monotherapy as first-line therapy for metastatic breast cancer. Conversely, vinorelbine is less often used in this patient population and has a market share of approximately 14% (Data on file RXUKDONF001182011)

This information from NICE guidelines (NICE CG81 2009), the Xeloda SPC and market research highlights the prominent position in UK clinical practice for capecitabine therapy in patients who are unsuitable for taxane re-challenge in the metastatic setting. As highlighted by the RIBBON-1 data, the addition of bevacizumab to capecitabine monotherapy significantly improves the PFS and OS in this patient population and counteracts the poor prognosis associated with patients who have received a prior adjuvant taxane.

Relevance of outcomes of the RIBBON-1 study to the benefits for patients in clinical practice

The RIBBON-1 study's primary outcome was to evaluate progression free survival (PFS) in the first-line treatment of metastatic breast cancer, in patients receiving capecitabine plus placebo versus capecitabine plus bevacizumab.

Cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (Helgeson & Tomich 2005); the most important distress factor among cancer survivors was found to be the fear of disease progression (Herschbach, Keller, Knight, Brandl, Huber, Henrich, & Marten-Mittag 2004). Therefore, the major objective of each successive line of therapy, in addition to extending OS, is to induce and maintain disease remission (ie PFS) for as long as possible.

Relevance and validity of subgroup analysis

As outlined in the decision problem, patients who have received a prior adjuvant taxane have a poor prognosis and represent a very significant unmet clinical need for new therapies. These patients tend to relapse rapidly after their response to first-line therapy and also tend to have short overall survival; this is evidenced by capecitabine and placebo results for such patients in the RIBBON-1 trial. Data from RIBBON-1 demonstrates that patients who had received a prior taxane have extended progression free and overall survival with capecitabine in combination with bevacizumab. The addition of bevacizumab to capecitabine in these patients raised their overall survival and PFS above a level found in the ITT population with bevacizumab and capecitabine, thus counteracting the poor prognosis of these patients (PFS Capecitabine and bevacizumab arm: ITT = 8.6 months, prior taxane = 8.7 months, OS: ITT = 25.7 months, prior taxane = 28.4 months)

Although subgroup analysis in the RIBBON-1 trial was taken from an un-stratified population of patients, several factors increase the validity of using these subgroup data. The first is the sizeable number of patients included in the subgroup analysis; the 245 patients analysed from this population is comparable to small phase III study. The second factor is that all bevacizumab RCTs demonstrated a similar phenomenon of substantial PFS / overall survival gains from bevacizumab treatment in patients who have previously received a taxane (Data on File 2011;Glaspy et al. 2010;Miles et al. 2010). Table 8 demonstrates the PFS increase in prior taxane treated patients who have received bevacizumab and chemotherapy compared to chemotherapy alone. These results also demonstrate that the PFS in prior taxane treated patients is increased to a similar level to the ITT population of these trials, suggesting that these particularly poor prognosis patients benefit especially from bevacizumab treatment.

Table 8: Comparison of treatment efficacies in 3 RCTs containing bevacizumab (from O'Shaughnessy 2009)

	ITT population Median PFS (months)		Prior taxane Median PFS (months)	
	placebo	**bevacizumab**	**placebo**	**bevacizumab**
E2100 – paclitaxel ± bev/placebo	5.8	11.3	5.8	13.1
AVADO – docetaxel ± bev/placebo	7.9	8.8	6.7	8.6
RIBBON-1 – capecitabine ± bev/placebo	5.7	8.6	4.2	8.7

(Data on File 2011;Gray et al. 2009;Shaughnessy et al. 2009)

To verify this effect an individual patient meta-analysis of 311 prior taxane treated patients arose from the three bevacizumab RCTs (E2100, AVADO, and RIBBON-1) and demonstrated the clear benefit of bevacizumab in addition to first-line taxane therapy in mBC patients who had received a prior taxane (Miles 2010). The meta-analysis assessed patients who previously received a prior adjuvant taxane; 177 patients received bevacizumab with either paclitaxel, nab-paclitaxel or docetaxel therapy, and the remaining 134 patients were treated with a taxane alone. In taxane re-treated patients, the median overall survival was significantly increased with the addition of bevacizumab to a taxane; from 21.3 months with taxane alone (n=134) to 26.9 months with taxane plus bevacizumab (n=177) (HR=0.73, 95% CI: 0.55-0.97, p=0.030). The progression free survival in patients receiving a taxane alone was 6.2 months which significantly increased to 10.7 months when patients were given a taxane plus bevacizumab (HR= 0.47, 95% CI: 0.35-0.62, p<0.0001). Data from this large meta-analysis supports the concept that bevacizumab in combination with chemotherapy can benefit poor prognosis patients who have been treated with a prior adjuvant taxane.

Three phase III RCTs all demonstrate that patients who have received a prior taxane benefit from bevacizumab in combination with a taxane therapy. The meta-analysis of these patients confirms the significant overall survival and PFS benefit observed in the RIBBON-1 trial. Experience from nearly 600 patients in three different studies across three different therapies adds weight to the concept that prior taxane treated patients particular benefit from bevacizumab plus chemotherapy.

5.10.4 Identify any factors that may influence the external validity 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 patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The decision problem in this submission states the need to find effective treatments for patients who are unsuitable for anthracycline and taxane treatment. The RIBBON-1 trial met the objective of this submission by investigating the safety and efficacy of capecitabine in combination with bevacizumab in metastatic patients. Subgroup data from a large population of patients (n=245) who have had a prior adjuvant taxane were analysed. This subgroup analysis showed that patients who had a prior adjuvant taxane and subsequently received capecitabine monotherapy had a shorter PFS than patients who were in the ITT population receiving the same treatment. Importantly, in patients who have had a prior taxane, the addition of bevacizumab to capecitabine increased the PFS and OS benefit to the level of the ITT population, demonstrating the efficacy of bevacizumab in this poor prognosis patient population.

In the RIBBON-1 study the concept of investigating capecitabine and bevacizumab efficacy in patients who have had a prior taxane was valid due to three main factors.

Firstly, NICE guidelines state that docetaxel should be used in the first line mBC patient population, followed by a choice of either capecitabine or vinorelbine in the second line setting (NICE CG81 2009). With patients who have already received an adjuvant taxane (such as docetaxel), capecitabine is often the first-line treatment of choice. Secondly, UK market research suggests that approximately half of patients unsuitable for taxane therapy will receive capecitabine first line after a prior adjuvant anthracycline and taxane (Data on File, RXUKDONF00118). Thirdly, the Xeloda (capecitabine) licence for mBC states that it should be used specifically in mBC patients after the failure of taxanes and an anthracycline-containing chemotherapy regimen. Therefore, the therapy used in the RIBBON-1 trial was appropriate for the treatment of patients who have received a prior taxane, and is accordance with usage in UK clinical practise.

The RIBBON-1 trial was an international study across 178 centres, at least 30 patients in the capecitabine and bevacizumab arm were from UK centres, suggesting that some of the patient population was representative of the UK population. The

majority of sites (113) were in the US: many US patients share similar racial (genetic) profiles with UK patients.

The decision problem outlined the need for effective treatment in patients who have received a prior taxane and anthracycline. Data for these pre-planned investigations were from a large unstratified analysis of subgroups (n=245). However, data from this trial is in line with sub-group analyses from other bevacizumab RCTs and a meta-analysis in first line metastatic breast cancer (Miles et al 2010a, Miles et al 2010b, Gray et al 2009, Data on File RXUKDONF00003, O'Shaughnessy et al 2009, Glaspy et al. 2010).

What proportion of the evidence base is for the dose(s) given in the SPC?

All patients receiving bevacizumab in RIBBON-1 received the dose shown in the SPC. The licensed dose for the treatment of metastatic breast cancer with single agent capecitabine in the UK is 1250mg/m^2, given twice daily (bd) for 14 days of a 21 day cycle, however, in the RIBBON-1 study the dose utilised was 1000mg/m^2 (bd) at the same administration frequency. Market research has shown that over 50% of UK clinicians use a capecitabine starting dose of 1000mg/m^2 (bd) or lower (Market Research, Data on File RXUKDONF00146).

There is a paucity of randomised, controlled data comparing the licensed dose with a lower starting dose of capecitabine; however, there are several datasets showing that a lower starting dose of 1000mg/m^2 (bd) is well tolerated and highly active (Zielinski et al. 2010).

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 **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 as in section 9.10, appendix 10.**

Embase (EMYY), Embase Alert, (EMBA), Medline (MEYY), Medline in Process (MEIP), EconLIT and NHS EED were searched for studies assessing the cost-effectiveness of bevacizumab plus capecitabine versus capecitabine alone. The search was designed to evaluate whether de novo modelling was necessary in order to answer the decision problem. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, EMBA, MEYY and MEIP whilst NHS EED was searched using The Centre for Reviews and Dissemination's website (University of York 2011) and Econ LIT was searched (The American Economic Association & EconLIT 2011), accessed on 2nd December 2011.Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (Table 9). If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 9: Inclusion and Exclusion criteria for cost-effectiveness studies

Parameter	Inclusion Criteria	Exclusion Criteria
Population	Previously untreated advanced breast cancer patients	Non-breast cancer patients, previously treated patients
Intervention	Bevacizumab with Capecitabine	-
Comparator	Capecitabine	-
Outcome	Cost per QALY gained, Cost per LY gained	-
Study Design	Economic Evaluations (cost effectiveness analyses, cost utility analyses, cost minimisation analyses)	RCTs, Observational Data, Budget Impact Assessments

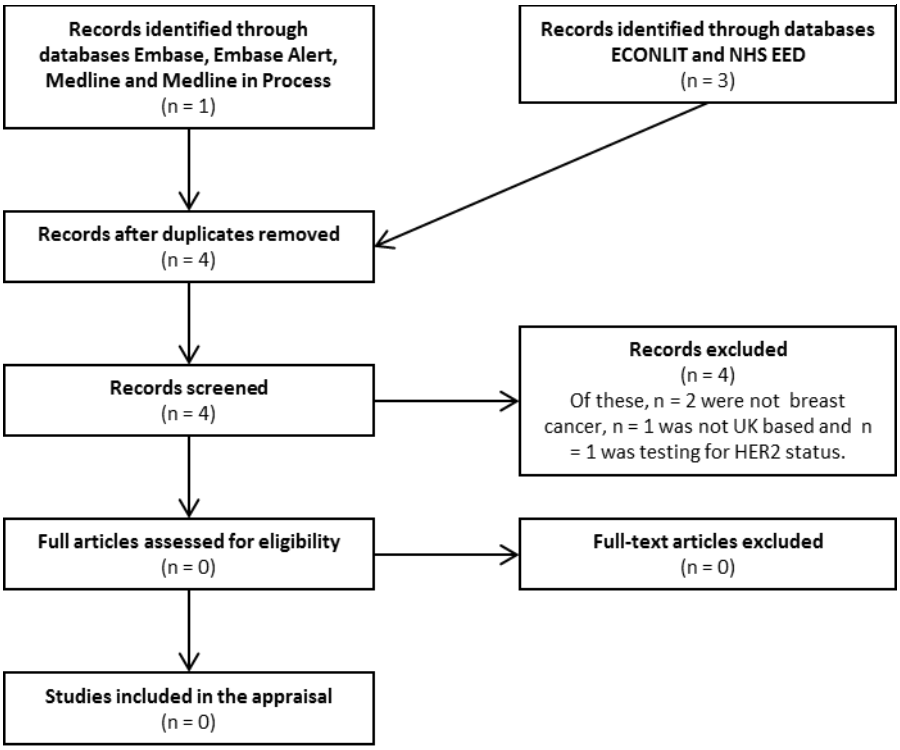
Table 10: PICOS exclusion criteria for cost-effectiveness studies

Criteria	Exclude if it fits following PICOS criteria
Population	Previously treated metastatic breast cancer patients
Intervention	Does not assess at least one of the regimens of interest
Comparator	
Outcomes	
Study Design	Not a cost-utility analysis (i.e. reviews, clinical trials, burden of illness studies)

The above methodology is founded on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008). The objectives of the search, and the inclusion criteria and exclusion criteria defined as a product of those objectives, were clearly aligned with the decision problem.

No cost-effectiveness studies were found comparing bevacizumab plus capecitabine to capecitabine in first-line untreated advanced breast cancer.

Figure 9: PRISMA Flow showing economic studies identified through searching of the databases



Description of identified studies

6.1.2 **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. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.**

No relevant cost-effectiveness analyses were identified.

6.1.3 **Please provide a complete quality assessment for each cost-effectiveness study identified.**

No studies were found.

6.2 De novo analysis

Patients

6.2.1 **What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? 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? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.**

The economic evaluation was conducted on the patient population reflected in the licences for capecitabine and for bevacizumab combination with capecitabine (i.e. patients receiving first-line therapy for HER2- metastatic breast cancer, who have relapsed after receiving taxane and anthracycline adjuvant therapy (failed these regimens) and for whom further anthracycline or taxane therapy is not considered appropriate. All efficacy and treatment duration parameters were derived from patient-level data of a defined subset of the ITT population in the capecitabine cohort of the RIBBON-1 RCT described in Section 5.3 (i.e. patients who had previously received a taxane before study entry).

Table 11: Comparison of patient cohorts in capecitabine arm of RIBBON-1

Cohort	Bevacizumab + capecitabine	Placebo + capecitabine
ITT	409	206
Prior taxane-treated patients	161	81

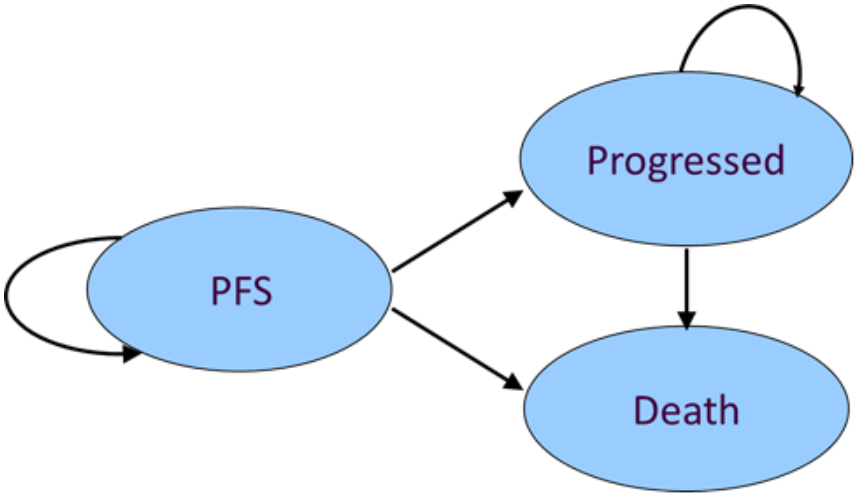
Model structure

6.2.2 **Please provide a diagrammatical representation of the model you have chosen.**

A 3 state model, founded upon the PFS and OS endpoints of the RIBBON-1 study, was constructed in Microsoft Excel. All patients enter the model in the progression free survival (PFS) health state (consistent with the RIBBON-1 study) and in each month can either progress to a 'worse' health state (i.e. from PFS to progressed

disease (PD) or from PD to Death) or remain in the same health state. Figure 10 below demonstrates this model structure in terms of the health states utilized.

Figure 10: Model Schema



6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The model structure is fully aligned with two of the primary objectives of treatment in mBC; namely:

- Prolonging life
- Delaying disease progression

This model structure and the health states utilised are typical of modelling in metastatic oncology and have been utilised in numerous NICE appraisals including those specifically in metastatic breast cancer (Fleeman, Bagust, Boland, Dickson, Dundar, Moonan, Oyee, Blundell, Davis, Armstrong, & Thorp 2010;Rodgers et al. 2010).

6.2.4 Please define what the health states in the model are meant to capture.

The health states utilised in the model are those typically utilised in the modelling of metastatic oncology. The PFS health state is designed to capture an mBC patient's relatively high 'quality of life period' prior to their disease progression. The PD state is designed to capture the relatively poor 'quality of life phase' following disease progression/relapse.

6.2.5 **How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.**

The model is a 3 state model of the kind typically utilised in the modelling of metastatic cancer. As noted previously this structure captures both the length and quality of a patient's life via the dichotomisation of a patient's time alive into a relatively high quality of life 'pre-progression' phase and a lower quality of life post-progression phase. The survival data from the capecitabine arm of RIBBON-1 was utilised to inform the disease progression of the comparator arm.

6.2.6 **Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.**

Table 12: Key features of analysis

Factor	Value	Justification	Reference
Time horizon	15 Years	99.9% patients in bevacizumab arm absorbing 'death' state at this point – adequate to capture complete differences between comparators (as per reference case)	Economic model + NICE Guide to Methods (NICE 2008)
Cycle length	1 month	To facilitate simple calculation of QALYs and LYs as per reference case – Typical of metastatic cancer modelling	NICE Guide to Methods (NICE 2008)
Half-cycle correction	Yes	As per NICE guide to methods	NICE Guide to Methods (NICE 2008)
Were health effects measured in QALYs; if not, what was used?	Yes	As per NICE guide to methods	NICE Guide to Methods (NICE 2008)
Discount of 3.5% for utilities and costs	Yes	As per NICE guide to methods	NICE Guide to Methods (NICE 2008)
Perspective (NHS/PSS)	Yes	As per NICE guide to methods	NICE Guide to Methods (NICE 2008)
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Bevacizumab

Bevacizumab in combination with capecitabine was modelled as administered in the RIBBON-1 study (i.e. bevacizumab 15 mg/kg every 21 days until disease progression or unacceptable toxicity or a maximum of 48 months treatment with 1000 mg/m^2 capecitabine administered twice daily for 14 days of each 21 day cycle followed by a 7 day 'rest' period until progression, unacceptable toxicity or a maximum of 48 months).

Capecitabine

Capecitabine monotherapy was modelled as administered in the RIBBON-1 study (1000 mg/m^2 capecitabine administered twice daily every day until progression, unacceptable toxicity or a maximum of 48 months of treatment). As noted in the clinical section this differs slightly from the SPC specified dose for capecitabine in which it is recommended that capecitabine be given at a dose of 1250 mg/m^2 (25% higher than the dose used in RIBBON-1). This divergence presents some difficulty in enabling a formal comparison with capecitabine monotherapy as typically administered in mBC (although market research suggests around a quarter of all capecitabine mBC patients receive treatment at a dose of 1000 mg/m^2). Given this difficulty and an apparent lack of network enabling the comparison of the two doses (Roche internal search) in the base-case analysis the 1000 mg/m^2 dose was modelled with the 1250 mg/m^2 dose modelled in sensitivity analysis under the assumption of equivalent efficacy between the 1000 mg/m^2 and higher dose. It was determined that the 1000 mg/ m^2 dose rather than the 1250 mg/ m^2 dose should be modelled for the base-case as if the 1250 mg/m^2 dose were to be modelled under the assumption of equivalent efficacy between the dosing regimens it would in effect be dominated by the 1000 mg/ m^2 regimen (i.e. would be more expensive yet no more effective) and so the comparison made would not be on the efficiency frontier.

Vinorelbine

Market research conducted on by Synovate in 2010 has shown that vinorelbine is rarely utilised in the NHS for this indication (Roche data on file, Synovate 2010). The research indicated that capecitabine holds a market share approximately 5 times that of vinorelbine and so vinorelbine was not felt to be an appropriate comparator. However, the cost-effectiveness of bevacizumab and capecitabine against vinorelbine was explored in a scenario analysis where vinorelbine was assumed to have equivalent efficacy and safety profile to capecitabine, with different costs of acquisition and administration (NICE CG81 2009).

6.2.8 **Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators.**

Treatment with bevacizumab in combination with capecitabine or with capecitabine alone is continued until disease progression or unacceptable toxicity. In the modelled base-case the treatment duration observed in the study was utilised to determine the expected cost of treatment with each regimen (in terms of both drug and administration costs). The original variable used for TTOT is 'months from start pla/Bev to end of study treatment'. A survival curve for patients remaining on treatment was constructed (Section 6.5.5.5) under the following conditions:

- If observed TTOT <PFS, then TTOT is an event (observed), and not censored.
- If observed TTOT greater or equal to PFS then 2 possibilities :
    - If PFS is an event (observed, not censored), then TTOT is set to be =PFS, and is an event too.
    - If PFS is censored (not observed in the trial), then TTOT is also censored at the time of PFS.

The cost of monitoring patients for disease progression via a hospital visit and CT scan every 3 months is incorporated into the economic model (see section 6.5).

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

The most recent data-cut of the RIBBON-1 RCT (23/02/2009) was used in the model.

Transition from PFS

The proportions of patients who are progression-free in each month were taken directly from Kaplan Meier survival curves for either treatment arm in RIBBON-1. PFS is defined as the time from randomisation until the first date that recurrent or progressive disease was objectively documented by the Independent Review Facility (IRF) or death within 84 days of the last study treatment. The number of patients in each treatment arm dying from any cause while in PFS was used to derive a constant rate and probability of mortality (Table 13). In the model, the rate of mortality from the progression-free state was assumed to be at least as great as the underlying sex- and age-related mortality in the general population.

Table 13: Monthly mortality rates and probabilities from RIBBON-1

	BEV + CAP	**CAP**
Number of PFS Deaths	7	3
PFS Person-Months	1324.76	467.36
Monthly Rate of PFS Deaths	0.00528	0.00642
Monthly probability of Death	0.00527	0.00640

Those not transitioning to the death state from PFS were assumed to have progressed disease.

Transition from PD

A number of tunnel states were generated for patients within PD according to the time spent with progressed disease. Patients who enter PD experience an increasing probability of dying in each month based on an extrapolation of the survival data for progressed patients.

Since the cumulative hazard plots for post-progression survival for each arm did not appear to be linear, using a typical exponential function to describe the probability of death would have been inappropriate.

Overall Survival

Mean overall survival is an output of the model and is the sum of mean duration of PFS and mean duration of PD. The trial design of RIBBON-1 allowed patients to receive bevacizumab (according to the consulting physician's discretion) post-progression, regardless of which treatment arm they had been randomised to (Table 14).

Table 14: Use of bevacizumab post-progression in RIBBON-1

	ITT capecitabine	**Prev chemo capecitabine**	**Prev taxanes capecitabine**
Overall number of patients (placebo/bev)	201/404	152/285	84/161
Placebo crossing over	120(59.7%)	89(58.5%)	44(52.4%)
Bevacizumab crossing over	184(45.5%)	132(46.3%)	72(44.7%)

This has the potential to introduce a bias in the estimation of the treatment effect towards the null hypothesis i.e. patients randomised to the control arm may have a prolonged survival than they would have done if they had not received the study drug after disease progression and results in a reduction in the apparent treatment effect. A number of methods have been developed to account for and correct for this situation, each with its own strengths and limitations. In this particular case, the effect of treatment cross-over has been addressed using the Rank Preserving Structural Failure Time (RPSFT) Model.

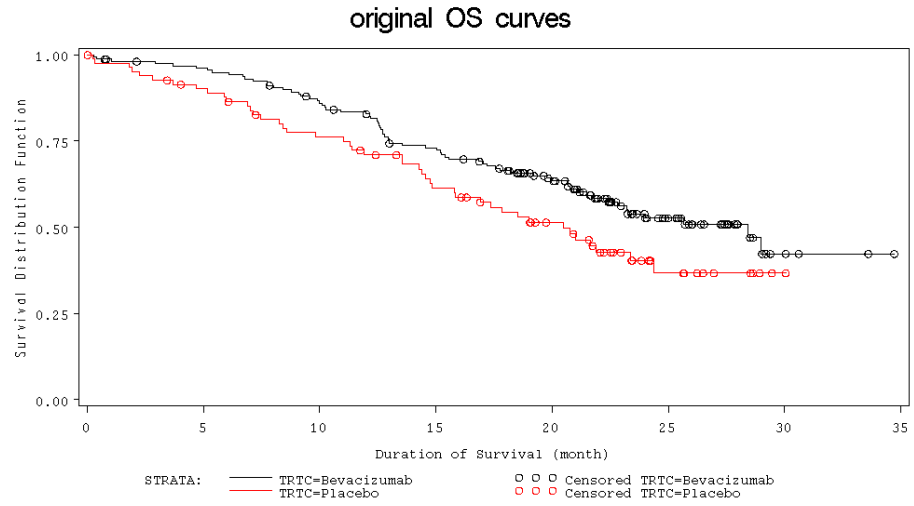
The RPSFT model relates observed failure times (Ti) and treatment histories (Ti(off) and Ti(on), as time spent off and on treatment, respectively) to failure times that would have been observed if the patient had not been treated (Ui):

$$Ti = Ti(off) + Ti(on)$$

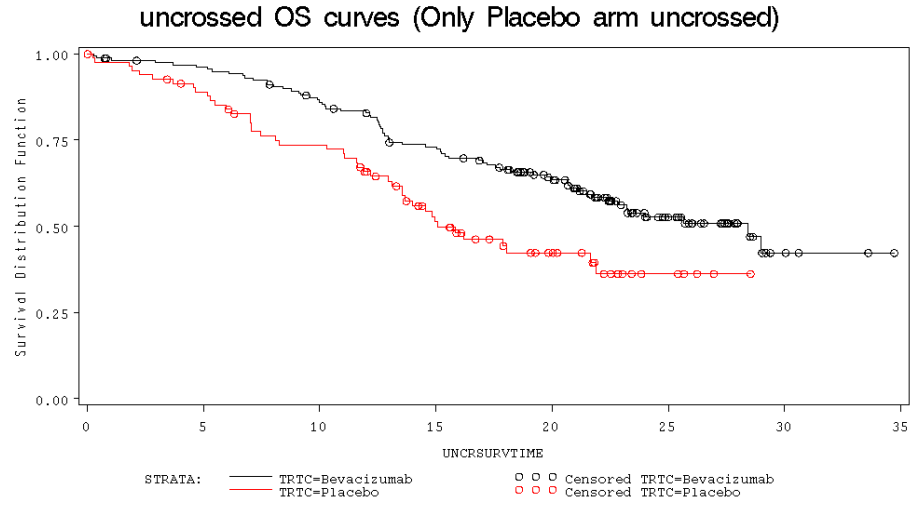
$$Ui = Ti(off) + [\exp(psi^*) \times Ti(on)]$$

The adjustment factor, exp (psi*), is the rate at which lifetime is 'used up' while on treatment compared to off treatment and implies a benefit of treatment when less than 1. For example, if exp(psi*) = 0.8, 1 day in treatment yields 0.2 additional days of survival compared to no treatment. The adjustment factor is estimated by finding the value which provides the highest p-value between the treatment arms depleted of treatment effect (i.e. when the distribution of the Ui are identical between treatment arms). The impact of this process on the Kaplan-Meier overall survival curves for treatment and placebo arms is demonstrated in Figure 11.

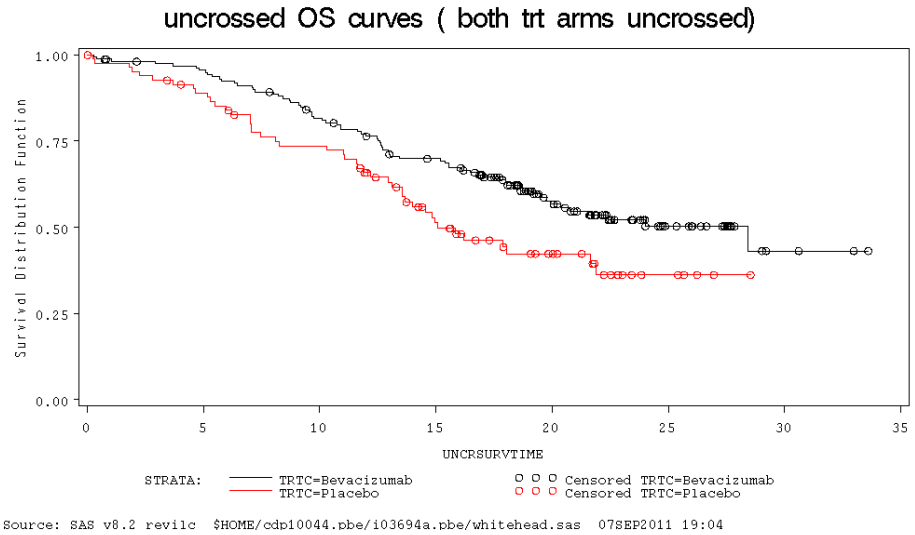
Figure 11: Impact of RPSFT on OS curves



Source: SAS v8.2 revilc $HOME/cdp10044.pbe/i03694a.pbe/whitehead.sas 07SEP2011 19:04



Source: SAS v8.2 revilc $HOME/cdp10044.pbe/i03694a.pbe/whitehead.sas 07SEP2011 19:04



6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Other than mortality rates for patients in PFS (see section 6.3.3) transition probabilities were not explicitly used within the model with the proportion of patients in each health state at each given month determined directly via parametric fitting of the survival curves from the RIBBON-1 study.

6.3.3 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.

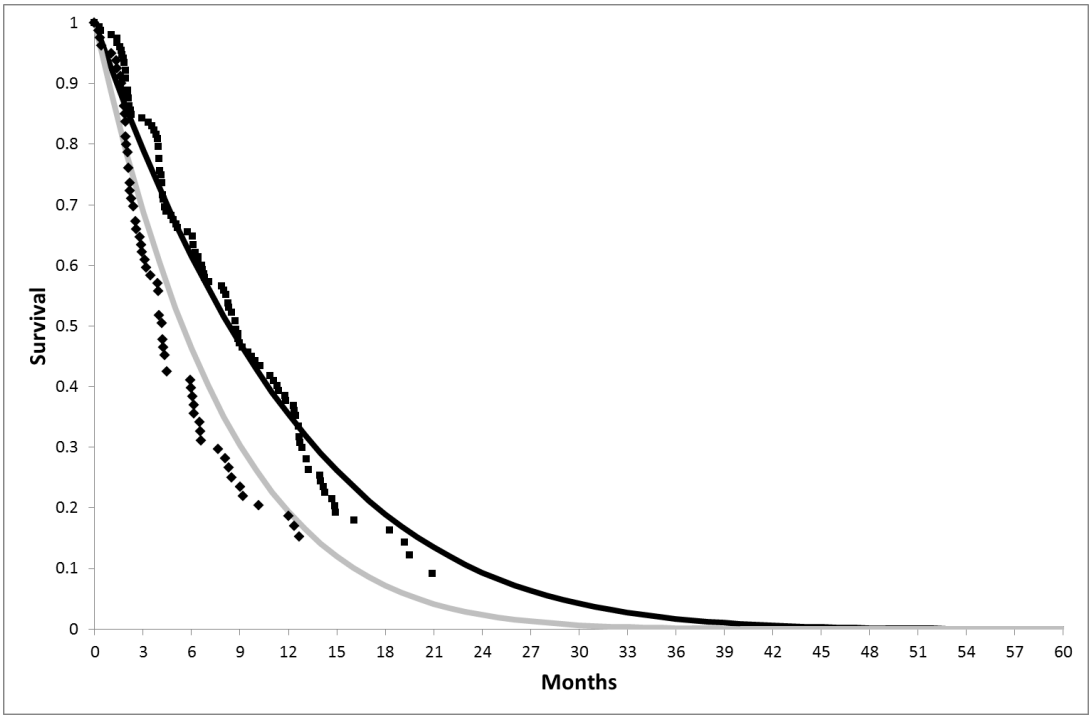
PFS

The PFS curve from the RIBBON-1 study was fitted parametrically with a range of different functions (see section 6.3.7). Of the 6 functions fitted, the exponential function (in which the hazard and probability of an event occurring is constant over time) was not determined to be the best fit, with the Gompertz function favoured according to standard statistical tests (Table 15). However, this approach appears to over-estimate time in PFS for the comparator arm (from months 3-12) and is a poor visual fit for the treatment arm from 12 months onwards (Figure 12).

Table 15: Statistics of parameter-fitting to observed PFS Kaplan Meier curves

MODEL	BIC	AIC
Gompertz	600.8857668	590.3819922
loglogistic	616.9596	606.4558254
lognormal	620.4338311	609.9300565
gamma	624.8187848	610.813752
Weibull	637.6289555	623.6239227
exponential	636.3769626	629.3744462

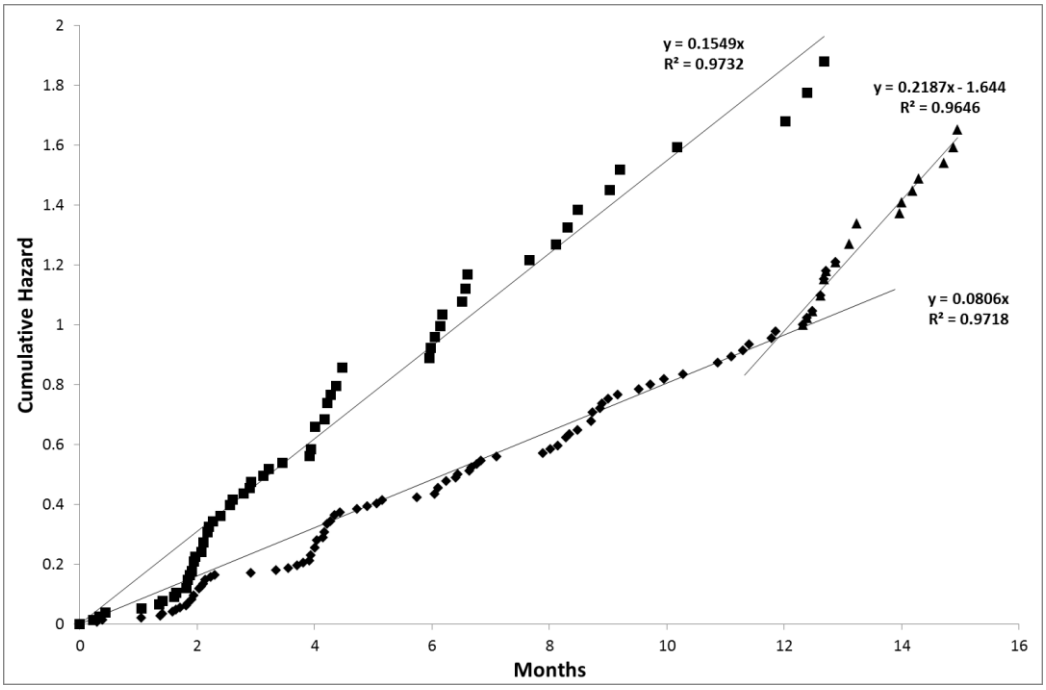
Figure 12: Observed (markers) and modeled (line) PFS assuming a Gompertz function.



A cumulative hazard plot allows one to present time to event data in a manner that enables relatively clear assessment of the way in which the hazard (instantaneous risk) of an event changes over time (the absolute hazard). It can be generated by plotting the negative log of the Kaplan-Meier (KM) survival probability at each time point. A completely straight cumulative hazard plot would indicate that the absolute hazard of an event occurring is constant over time and that therefore an exponential function would be an appropriate fit for extrapolation (in which the straight line is extrapolated). If two defined constant hazard periods are observed (i.e. the curve appears to be a joining of two straight lines with different slopes) then it may be more appropriate to utilise two exponential functions with the latter 'stabilised' hazard utilised for extrapolation (i.e. if there is a 'kink' in the curve one extrapolates with the straight line observed after the kink).

In order to more accurately model the observed time spent in PFS it was assumed that the cumulative hazard plot for the bevacizumab arm of RIBBON-1 was composed of 2 curves as shown in (Figure 13). This approach allows for the noticeable change in slope seen at approximately 12 months and does not disregard the behaviour observed for the 44 patients remaining in PFS at 12 months, representing more than 25% of the original cohort (N=161).

Figure 13: Cumulative Hazard plot of PFS



Note: The RIBBON-1 protocol stipulated assessment by CT scan every 9 weeks to monitor progression of disease and accounts for the step-wise increase in cumulative hazard seen at approximately 2 monthly intervals.

The base case model therefore used the probability of remaining in PFS observed in the RIBBON-1 trial for each arm directly until the twelfth month of treatment, after which the survival curve is extrapolated according to an exponential function.

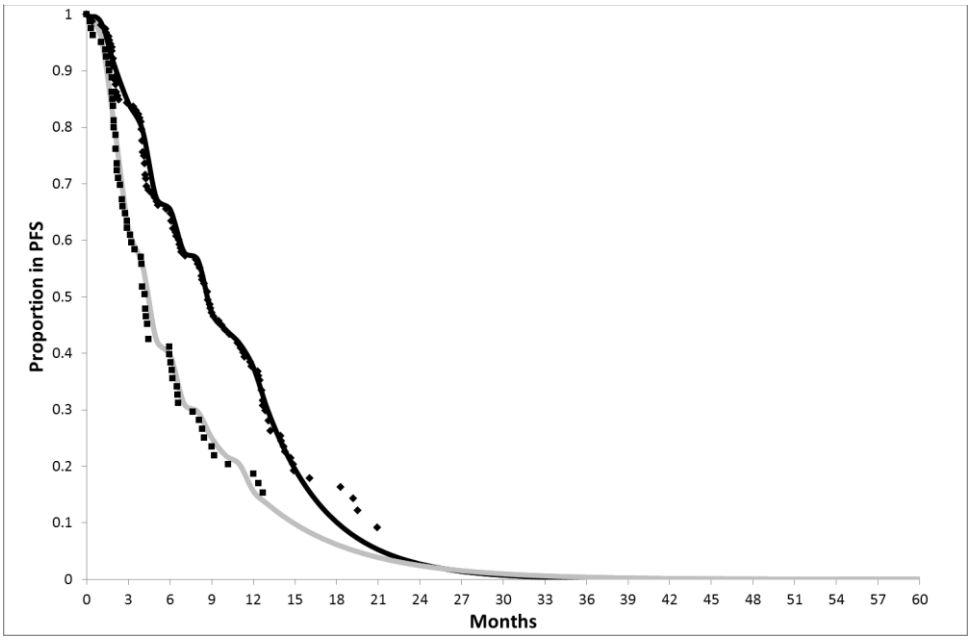
Bevacizumab arm:

Probability of remaining in PFS after 12 months of treatment = exp (-(0.2187 x months – 1.644))

Capecitabine arm:

Probability of remaining in PFS after 12 months of treatment = exp (-(0.1549 x months))

Figure 14: Modeled PFS curves as used in the model



Mortality after Progression

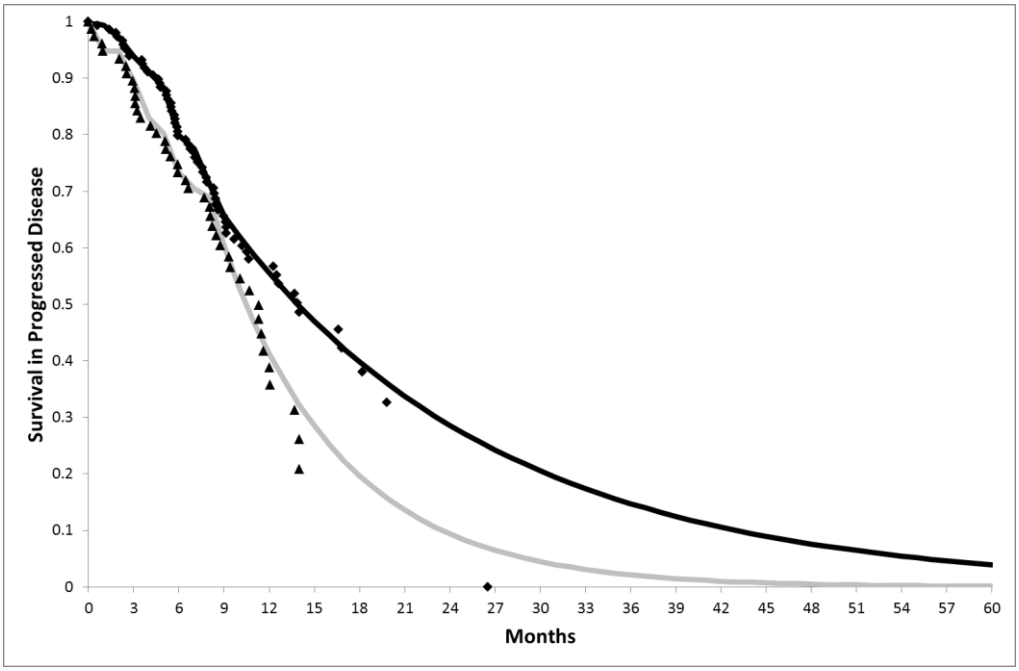
The cumulative hazard plot of mortality from PD is not linear and, according to standard statistical tests (Table 16) is best modelled by a Gompertz function.

Table 16: Statistics of parameter-fitting for survival in PD

MODEL	BIC	AIC
Gompertz	422.8492506	412.5090385
Loglogistic	458.5537018	448.2134897
Gamma	462.8616899	449.0747404
Weibull	463.0203241	449.2333746
Lognormal	465.5369095	455.1966974
Exponential	470.4446117	463.5511369

However, with visual inspection of the fits, none of these models had face-validity and therefore the base case model used the probability of remaining in PD observed in the RIBBON-1 trial for each arm directly until patients had spent a total of 12 months with progressed disease, after which the survival curve is extrapolated according to an exponential function (Figure 15).

Figure 15: Comparison of observed and modelled survival in PD



New patients with progressed disease enter an array of temporary states arranged so that each state has a transition only to death or the next temporary state; a so-called tunnel state.

The overall survival predicted by the model (through the combination of mortality through PFS and mortality after progression) was compared against the survival observed in the trial and results are shown in Section 6.7.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No surrogate outcomes were utilised to derive final clinical outcomes. Both PFS and OS are clinically relevant outcomes that are highly relevant to a patient's length and quality of life.

6.3.5 **If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[1]:**

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were consulted in the development of this specific economic model. Roche has held two advisory boards to obtain validation of the assumptions and inputs utilised in metastatic breast cancer economic models recently (bevacizumab in combination with a taxane and trastuzumab in combination with an aromatase inhibitor) and so it was felt that further validation of the clinical inputs utilised in this appraisal was not warranted.

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Summary of selected values

6.3.6 **Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.**

Table 17: Summary of variables applied in the economic model

Variable	Value	Reference to section in submission
Age	53.36 years	Patient characteristics section 5.3.4
Weight	72.1 kg	
Height	160.89 cm	
Utility		
PFS Bev+Cap arm	0.784	Section 6.4.6
PFS Cap arm	0.774	
PD	0.496	
Costs		
Monthly Cost of Bevacizumab	£3,689.12	Section 6.5.5.1
Monthly Cost of Capecitabine (in Bev arm)	£323.56	Section 6.5.5.2
Monthly Cost of Capecitabine (in Cap arm)	£312.41	Section 6.5.5.2
First Month Cost of Bevacizumab Administration and pharmacy	£338.94	Section 6.5.5.3
Subsequent Month Cost of Bevacizumab Administration and pharmacy	£196.09	Section 6.5.5.3
Monthly Cost of Capecitabine Administration and pharmacy	£9.88	Section 6.5.5.4
Monthly Cost of Capecitabine Administration and pharmacy	£255.32	Section 6.5.5.4
Total monthly cost of PFS	£263.55	Section 6.5.6.1
Total monthly costs of PD	£804.00	Section 6.5.6.2

6.3.7 **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 intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.**

See Section 6.3.3.

6.3.8 **Provide a list of all assumptions in the de novo economic model and a justification for each assumption.**

1. It was assumed that the Lloyd utility values for PFS and PD as modified by Fleeman et al. to represent the utility of HER2+/HR+ mBC patients receiving first line lapatinib + letrozole or letrozole monotherapy would similarly hold for HER2-negative mBC patients receiving BX or X as first line treatment for the metastatic disease(Fleeman, Bagust, Boland, Dickson, Dundar, Moonan, Oyee, Blundell, Davis, Armstrong, & Thorp 2010). As these utility values have recently been utilised in an MTA on mBC technologies it seemed reasonable to utilise these values again.

2. It was assumed that unused bevacizumab in opened vials would not be available for subsequent administrations and would be destroyed. As bevacizumab is not currently approved by NICE in any of its indications it was felt that assuming vial sharing (and therefore reduced wastage) may seem unreasonable and so in the base-case model the assumption of 100% of unused drug wastage was made. As the government's cancer drugs fund (CDF) has prompted use of bevacizumab within the NHS it is likely that vial sharing may take place within the NHS and so this assumption can be regarded as conservative.

3. It was assumed that 1000 mg/m^2 administered capecitabine was the comparator of interest. Whilst this assumption is clearly contentious due to the SPC of capecitabine stating a higher dose should be utilised the results of the economic analysis undertaken demonstrate that the use of a 1000 mg/m^2 rather than 1250 mg/m^2 capecitabine administration schedule is unlikely to influence the likelihood of the appraisal committee approving BX as per its proposed licence extension.

4. It was assumed that the outcomes (PFS, OS, AEs) and time to off treatment (TTOT) patterns observed in RIBBON-1 would hold in clinical practice. Given that

RIBBON-1 is the only evidence base available to make the comparison this assumption is essential. As RIBBON-1 was a well conducted study conducted in part in Europe this seems reasonable.

5. Vinorelbine was assumed to have an equivalent efficacy and safety profile to capecitabine, with different costs of acquisition and administration as proposed in recent clinical guidelines from NICE (NICE CG81 2009).

6. Progressed Disease is assumed to entail the same costs and utilities regardless of first-line treatment. This seems reasonable given current clinical guidelines on treatment and management of metastatic disease (NICE CG81 2009).

7. Adverse events requiring treatment were assumed to occur in the first month of the model.

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 **Please outline the aspects of the condition that most affect patients' quality of life.**

Studies have found that cancer survivors whose disease recurs have a worse quality of life in most indices than those who remain disease-free (Helgeson & Tomich 2005) and the most important distress factor among cancer patients has been found to be the fear of disease progression (Herschbach, Keller, Knight, Brandl, Huber, Henrich, & Marten-Mittag 2004).

6.4.2 **Please describe how a patient's HRQL is likely to change over the course of the condition.**

Health-related quality of life is expected to decrease with each line of treatment failure due to disease progression.

HRQL data derived from clinical trials

6.4.3 **If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case.**

EQ-5D data was not collected in the RIBBON-1 study and therefore no HRQL data consistent with the NICE reference case was available.

Mapping

6.4.4 **If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.**

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was undertaken.

HRQL studies

6.4.5 **Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.**

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), Medline in Process (MEIP), EconLIT and NHS EED were searched for studies assessing utility values for different health states in mBC. The search was designed to evaluate all potentially relevant utility scores that have been used in metastatic breast cancer health technology evaluations. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, MEYY and MEIP whilst NHS EED was searched using The Centre for Reviews and Dissemination's website http://www.crd.york.ac.uk/crdweb/SearchPage.asp and ECON LIT was searched suing (The American Economic Association & EconLIT 2011) accessed on 2nd December 2011.Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see table below).

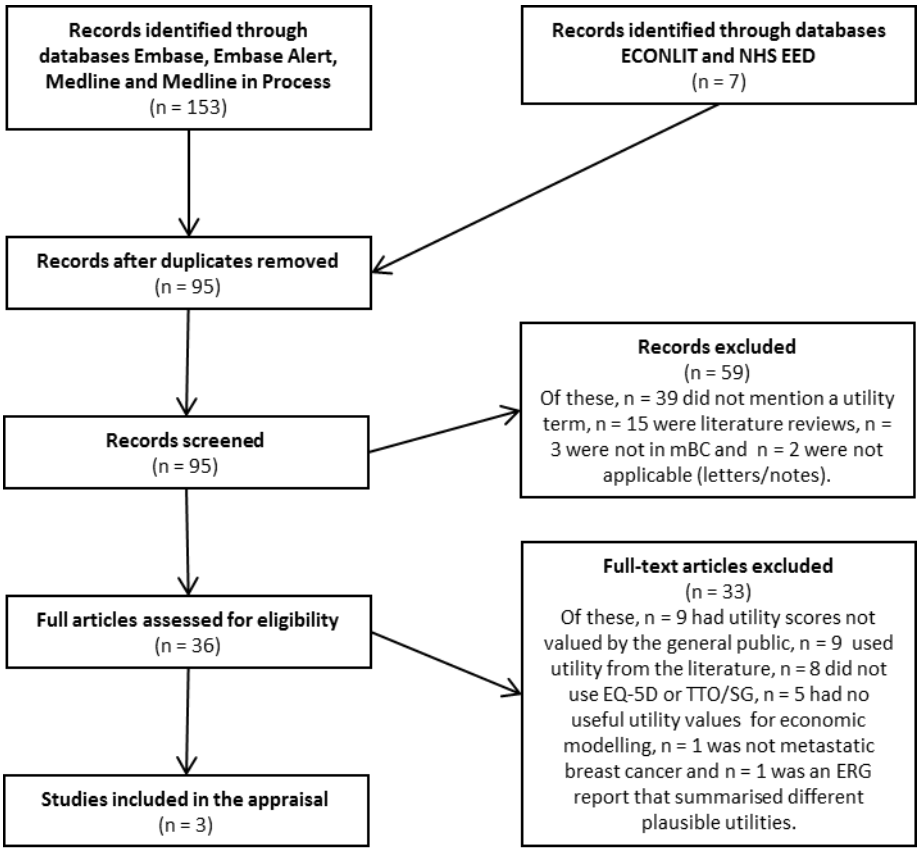
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria.

Table 18: Inclusion and Exclusion Criteria for Utility Studies

Inclusion Criteria	Exclusion Criteria
Metastatic or advanced breast cancer Health related quality of life QALY or quality adjusted life year SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL Utilities Time Trade Off or Standard Gamble	Review of studies already included Not QoL studies Utility value not elicited by the general public Not in metastatic/advanced setting No useful HRQoL/Utility values for economic modelling

In total 95 records were identified from 6 databases. Of these, 59 were excluded by the independent reviewers and 36 were deemed potentially relevant and read in full. Of these 36, a further 33 were excluded after being read, and 3 were included in the review (Dranitsaris et al. 2000;Leung et al. 1999;Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006)

Figure 16: PRISMA flow for utility studies identified through database searching



6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.

- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

The searches found 3 studies that measured utility values directly and that could potentially be used in our economic model. The table below briefly summarises the main characteristics of the 3 articles:

Table 19: Summary of the 3 utility articles deemed relevant from the systematic review

	(Dranitsaris, Leung, Mather, & Oza 2000)	**(Leung, Tannock, Oza, Puodziunas, & Dranitsaris 1999)**	**(Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006)**
Population	25 general public, 25 female health care professionals	25 health care workers and 25 breast cancer patients	100 general public completed study
Elicitation methods	TTO	TTO	SG
Data set	Vignettes of progression free survival	Vignettes of 3 treatments for mBC and side effects	Vignettes of mBC with different responses and side effects
Disease area/treatment	Advanced breast cancer	Metastatic breast cancer	Metastatic breast cancer
Utility estimate	PFS response to an AI public average = 0.8, nurse average = 0.74. PFS response to megestrol acetate = 0.8, nurse 0.67	PFS response to paclitaxel = 0.62 (0.61), response to docetaxel = 0.51 (0.49) and response to vinorelbine = 0.8 (0.77) *patients values in parentheses	PFS stable = 0.715, treatment response = +0.075, disease progression = -0.272, and other decrements for side effects.

Dranistaris et al. provide utility values from the TTO methods, using months instead of years to trade in (Dranitsaris, Leung, Mather, & Oza 2000). This is probably more appropriate than using years (the TTO standard is to use 10 years) as metastatic breast cancer patients typically have around 2 years of life. The study provides PFS estimates for 2 aromatase inhibitors and megestrol acetate for response to treatment, no response to treatment but response to chemotherapy and no response to

treatment and progression during chemotherapy. The notable values that could potentially be used in the model come from response to treatment which were 0.8 when valued by the public, and varied considerably when valued by health care professionals (0.78 for letrozole, 0.72 for anastrozole and 0.67 for megestrol acetate). Utility values are provided for a patient having not responded to one of the three named drugs (letrozole, anastrozole or megestrol) but having responded to subsequent chemotherapy - 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). These would not be useful for our model as we have no data on subsequent response rate to such chemotherapies within the pivotal study. Furthermore, the sample used is also quite small, and so the robustness of the 0.8 value estimated by the public for response to treatment is not sufficiently validated.

Leung et al. provide utility values for metastatic breast cancer patients' PFS having responded to 3 different types of treatment (paclitaxel, docetaxel and vinorelbine) (Leung, Tannock, Oza, Puodziunas, & Dranitsaris 1999). There was consistency between the general public valuations and breast cancer patients' valuations, with the latter being slightly lower in each case. There is considerable variation in the values estimated for the 3 treatments, and given this, and that none of the 3 treatments are of relevance, using an average of these utility values in the model would lack consistent validity.

Lloyd 2006 report the results of 100 participants asked to value various health states and side effects associated with metastatic breast cancer using the Standard Gamble technique (Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006). An overall value for PFS is found, and then deviations from this value (such as response to treatment, and progression of disease) are reported as incremental changes from this baseline utility value. Within our model we have no *a priori* knowledge that would suggest that responding to treatment with bevacizumab plus capecitabine is better than a response to capecitabine alone, it seems most appropriate to use a base case PFS utility value that has been derived from a large population, and then to adjust that base utility by response rate. Furthermore, the utility values from this study have been used in numerous health technology appraisals for metastatic breast cancer (Fleeman, Bagust, Boland, Dickson, Dundar, Moonan, Oyee, Blundell, Davis, Armstrong, & Thorp 2010).

6.4.7 **Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.**

No utility values were taken from RIBBON-1 (either directly via EQ-5D or via mapping).

Adverse events

6.4.8 **Please describe how adverse events have an impact on HRQL.**

Serious adverse events will result in either a short or long term detriment to health-related quality of life as identified in the utilities literature (Table 19) and summarized Section 6.4.9.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 **Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.**

A recent MTA for lapatanib and trastuzumab in combination with an aromatase inhibitor (AI) for the first line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2 (Fleeman, Bagust, Boland, Dickson, Dundar, Moonan, Oyee, Blundell, Davis, Armstrong, & Thorp 2010), contains utility estimates determined to be appropriate for use in mBC and are used here in preference to all other estimates identified in the systematic literature review described in Sections 6.4.5 and 6.4.6.

It should be noted that although the study by Lloyd et al is a large preference study designed to obtain UK-based societal preferences for distinct stages of mBC, the values derived from that study are subject to a number of caveats. Firstly, the health states used by the investigators were derived from literature reviews, exploratory interviews with physicians and an oncology focus group made up of specialist nurses rather than patient experiences. Secondly, the health states were gender neutral and there was no mention of *"cancer"* in the health state descriptions. Therefore these utility valuations of the general public may not fully reflect either the experiences of patients with cancer or the true preferences of the general public with respect to mBC. Nevertheless this study is regarded as the most useful evidence available that could help to inform this decision problem.

Calculation of Utilities

Utilities were calculated from the results of the mixed model analysis presented by Lloyd et al using the formula below:

Exp(sum_coefficients)/1+exp(sum_coefficients) (Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006)

The central estimates of the parameter coefficients (and their standard errors) are recorded in Table 20.

Table 20: Results of the mixed model analysis (Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006)

Parameter	Parameter estimate	Standard error
intercept	0.008871	0.3196
age	0.0239	0.006946
treatment response	0.4063	0.05521
disease progression	-1.1477	0.1031
febrile neutropenia	-0.6603	0.08501
diarrhoea and vomiting	-0.4629	0.09929
hand-foot syndrome	-0.5184	0.09929
stomatitis	-0.6634	0.09929
fatigue	-0.5142	0.09929
hair loss	-0.5086	0.09929

In order to maintain consistency with the EQ-5D UK tariff, the average age of respondents to the original study (Dolan et al. 1996) (i.e. 47 years) should be used to calculate utility values.

For patients who are in the PFS state it is necessary to calculate a treatment-specific weighted average of the model values for stable disease (calculated as 0.756) and treatment response (calculated as 0.823), based on the reported overall response rate (41.7% for bevacizumab and capecitabine, 25.97% for capecitabine alone) to verify in the RIBBON-1 trial. For patients in the PD state, a common health state utility value of 0.496 (se 0.160) was obtained for use in either treatment arm.

Table 21: Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
PFS			Utility values determined to be appropriate for use in mBC by Fleeman et al.(Fleeman, Bagust, Boland, Dickson, Dundar, Moonan, Oyee, Blundell, Davis, Armstrong, & Thorp 2010) in ongoing NICE mBC MTA assessing trastuzumab + AI, Lapatinib + AI and AI monotherapy in HR+/HER2+ mBC – Favoured over all other utility values identified in the search conducted.
Bevacizumab + capecitabine	0.784	Section 6.4.6	
Capecitabine	0.774		
PD	0.496		

A recent systematic review and analysis of utility studies in breast cancer (Peasgood, Ward, & Brazier 2010) has calculated regression models for early and metastatic BC according to several variables (treatment type, response to treatment, adverse events, valuation method and interviewee). Using the reported base case valuation method (standard gamble) and perspective (community) assumptions, the estimated utility values in this meta-regression are very similar to those presented by Lloyd et al (Lloyd, Nafees, Narewska, Dewilde, & Watkins 2006).

Since the utility values reported by Lloyd et al are not derived from patient experiences, a sensitivity analysis using data presented in Peasgood et al (Peasgood, Ward, & Brazier 2010) to derive estimated utilities from patients valuing their own health was conducted (see Section 6.6.9).

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[2]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions

[2] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were consulted in the development of this specific economic model. Roche has held two advisory boards to obtain to validation of the assumptions and inputs utilised in metastatic breast cancer economic models (including utility values) recently (bevacizumab in combination with a taxane and trastuzumab in combination with an aromatase inhibitor) and so it was felt that further validation on the utility values utilised in this appraisal was not warranted.

6.4.11 **Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?**

Patient experience is described in section 6.4.1. Regarding potential variation, this is addressed in section 6.4.14 below.

6.4.12 **Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?**

All relevant health effects identified in the literature have been taken into account.

6.4.13 **If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?**

The baseline quality of life has been assumed to be different in the 2 treatment arms of the economic evaluation. Patients in the PFS state are characterised as either responders, who have a slightly improved quality of life, or have stable disease (Section 6.4.9).

6.4.14 **Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.**

It has been assumed that HRQoL remains constant for the duration patients stay in each health state. No evidence has been found to suggest that HRQoL changes over time within each health state.

6.4.15 **Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.**

The methodology employed to analyse the published coefficients is described in Section 6.4.9.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 **Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.**

The recommended process for the clinical management of advanced breast cancer is the subject of a NICE clinical guideline (NICE CG81 2009) and this formed the basis of our costing assumptions for disease management. Please see Section 6.5.6 for details.

6.5.2 **Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.**

NHS reference costs are the most appropriate source of cost data for this appraisal.

Resource identification, measurement and valuation studies

6.5.3 **Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:**

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs

Embase (EMYY), Embase Alert (EMBA), Medline (MEYY), Medline in Process (MEIP), NHS EED and Econ LIT were searched for studies assessing resource

utilisation of patients with metastatic breast cancer. The search was designed to evaluate all potentially relevant cost studies that have been used in advanced metastatic breast cancer health technology evaluations, within the United Kingdom. The complete search strategy is provided in section 9.10. The methodology used was based upon on the methods outlined in the CRD's 'Guidance for undertaking reviews in health care' (2008).

Keyword strategies were developed using key references retrieved through initial scoping searches. No date limit was placed on the search undertaken. Dialogue DataStar was used to search EMYY, MEYY and MEIP whilst NHS EED was searched using The Centre for Reviews and Dissemination's website http://www.crd.york.ac.uk/crdweb/SearchPage.asp and ECON LIT was searched using (The American Economic Association & EconLIT 2011), accessed 2nd December 2011.Each search result's title and abstract were assessed for relevance according to the pre-defined inclusion and exclusion criteria (see table below).

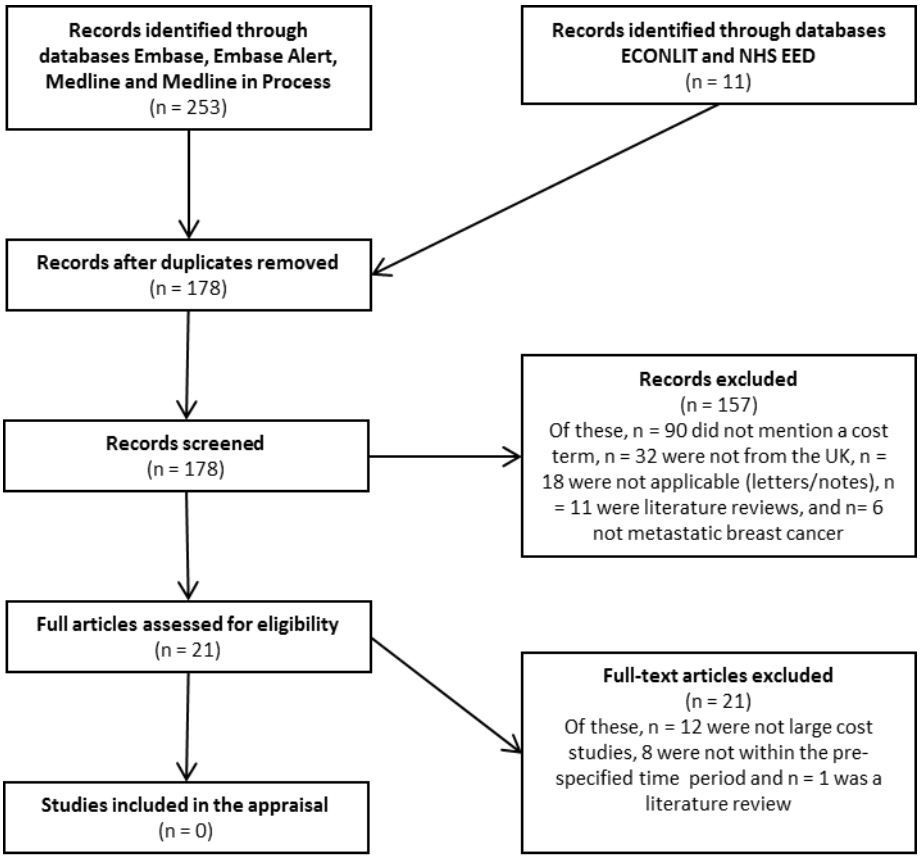
If a record was deemed potentially relevant it was retrieved in full and re-assessed against the inclusion/exclusion criteria:

Table 22: Inclusion and Exclusion Criteria for Resource Utilisation Studies

Inclusion criteria	Exclusion criteria
Advanced or metastatic breast cancer Resource utilisation from a UK NHS perspective	Early breast cancer Resource utilisation from a private/US setting – and any other non-UK country. Costs derived from studies more than 5 years old.

In total 178 records were identified from 6 databases. Of these, 157 were excluded by the independent reviewers and 21 were deemed potentially relevant and read in full. Of these 21 articles, zero articles made it through the second pass since no studies had calculated costs directly within the relevant time period.

Figure 17: PRISMA flow for cost studies identified through database searching



6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality whose opinion was sought

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

No clinical experts were consulted in the development of this specific economic model. Roche has held two advisory boards to obtain to validation of the assumptions and inputs utilised in metastatic breast cancer economic models (including resource use) recently (bevacizumab in combination with a taxane and trastuzumab in combination with an aromatase inhibitor) and so it was felt that further validation on the resource use inputs utilised in this appraisal was not warranted.

Intervention and comparators' costs

6.5.5 **Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.**

Table 23: Unit costs associated with the technology in the economic model (X=capecitabine monotherapy, BX=bevacizumab + capecitabine)

Items	Bev + Cap	Ref. in submission	Cap	Ref. in submission
Per Cycle Cost of Bevacizumab	£2,576.80	Section 6.5.5.1	NA	No Bev is given in Cap mono
Monthly Cost of Bevacizumab	£3,689.12	=(365.25/12) /21.26* £2,576.80	NA	No Bev is given in Cap mono
Per Cycle Cost of Capecitabine	£223.24	Section 6.5.5.2	£218.21	Section 6.5.5.2
Monthly Cost of Capecitabine	£323.56	=(365.25/12) /21.26* £223.24	£312.41	=(365.25/12)/21.26* £218.21

First Cycle Cost of Bevacizumab administration and pharmacy	£280.20	Section 6.5.5.3	NA	No Bev is given in Cap mono
Subsequent Cycle Cost of Bevacizumab administration and pharmacy	£137.20	Section 6.5.5.3	NA	No Bev is given in Cap mono
First Month Cost of Bevacizumab Administration and pharmacy	£338.94	Section 6.5.5.3	NA	No Bev is given in Cap mono
Subsequent Month Cost of Bevacizumab Administration and pharmacy	£196.09	Section 6.5.5.3	NA	No Bev is given in Cap mono
Per Cycle Cost of Capecitabine Administration and pharmacy	£6.90	Section 6.5.5.4	£178.33	Section 6.5.5.4
Monthly Cost of Capecitabine Administration and pharmacy	£9.88	Section 6.5.5.4	£255.32	Section 6.5.5.4
Total First monthly cost of regimen including drug, admin and pharmacy	£4,361.50	The sum of the constituent parts detailed above	£567.73	The sum of the constituent parts detailed above
Total Subsequent monthly cost of regimen including drug, admin and pharmacy	£4,218.65	The sum of the constituent parts detailed above	£567.73	The sum of the constituent parts detailed above

Please note for dose calculations the average cycle length observed in the trial of 21.26 days has been used rather than the per protocol 21 days per cycle. This is a conservative estimation since given that patients within the strict control of a trial are missing doses, they will most likely miss more days in real-life.

6.5.5.1 Bevacizumab drug cost:

Bevacizumab is administered by intravenous infusion once every 3 weeks at a dose of 15 mg/kg. For a 72.1 kg patient (the mean patient weight observed with RIBBON-1) this equates to a required dose of 1081.50 mg per dose.

15 mg/kg * 72.1 kg = 1081.50 mg

Bevacizumab can be purchased in two vial sizes at 25 mg/ml concentration (Joint Formulary Committee 2011):

- 4-ml (100-mg) vial = £242.66
- 16-ml (400-mg) vial = £924.40

A 72.1 kg patient would require a 2 x 400-mg vials and 2.82 x 100-mg vials to be administered which, depending on the centre's policy on vial sharing, may require the purchase of 2 x 400-mg vials and 3 x 100-mg vials (if no vial sharing is assumed) or 2 x 400-mg vials and 2.82 x 100-mg vials (if vial sharing is assumed and the centre utilizes the bevacizumab remaining in the vial). For the purposes of the base case it is assumed that no vial sharing will take place.

The expected per protocol per cycle cost of treatment with bevacizumab including consideration of wastage is therefore £2576.78.

£924.40 * 2 + £242.66 * 3 = £2576.78

On a monthly basis this amounts to a cost of £3,689.12.

£2,576.78 * (365.25/12)/21 = £3,689.12

In the RIBBON-1 study it was observed that despite the expected dose based upon patient weight at baseline being 1081.50 mg the average dose per administration over the course of the study was 1093.30 mg (perhaps due to frailer, light patients progressing more quickly than their heavier counterparts distorting the mean patient weight across the study away from that observed at baseline).

When no vial sharing is assumed the utilisation of the actual dose per administration rather than planned dose per administration has no impact upon the model as both the planned and observed dose equate to the same number of vials once rounded up. For the base-case analysis the actual dose was utilized with wastage assumed which (as noted above) equates to a cost per month of treatment of £3,689.12.

6.5.5.2 Capecitabine drug cost:

In RIBBON-1 1000 mg/m^2 oral capecitabine was administered twice daily until disease progression in both the monotherapy and combination therapy arms. The BSA of a patient is a function of their height and weight and so can be calculated based upon the mean weight and height observed in RIBBON-1. The average height of patients in RIBBON-1 was 160.89 cm whilst the weight was 72.10 kg. Using the formula of DuBois and DuBois hosted on the Cornell University medical college website (http://www.users.med.cornell.edu/~spon/picu/calc/bsacalc.htm) leads to a mean BSA of 1.7609 m^2.

$$(W^{0.425} \times H^{0.725}) \times 0.007184 = BSA$$

$$(71.45^{0.425} \times 160.59^{0.725}) \times 0.007184 = 1.7517$$

A 1.7517 m^2 patient therefore requires a dose of 1751.7 mg capecitabine twice daily for the first 14 days of each 21 day cycle.

Capecitabine can be purchased in two pack sizes (Joint Formulary Committee 2011):

- 60 x 150 mg tablets = £40.02
- 120 x 500 mg tablets = £265.55

Therefore for the purposes of the base-case model it is assumed a 1.7517 m^2 patient requires 3 x 500 mg tablets and 2 x 150 mg tablets at each dose (equalling a total dose of 1800 mg) at a cost of £7.97 per dose (of which there are 2 a day for the first 14 days of each 21.26 day cycle). This equates to a 'per cycle' cost of £218.21 (£7.97 x 2 x 14) and a monthly cost of capecitabine whilst on treatment of £312.41 (cost per cycle * (365.25/12)/21.

6.5.5.3 Bevacizumab administration and pharmacy cost

Bevacizumab is administered by intravenous infusion in a hospital on the first day of each 21.26 day cycle. There is a cost associated with both the pharmacy preparation of the infusion and the administration of the drug itself (typically within a hospital setting) that is incremental to the cost of preparing and delivering oral capecitabine alone.

The administration requirement for the first month is calculated as the full cost of the first cycle of chemotherapy (£271, [NHS Reference costs 2009/2010 (SB13Z): Deliver more complex Parenteral Chemotherapy at first attendance (Day case)]) plus 43.1% of the second cycle, or £59.22 (=0.431 x £128 [NHS Reference costs 2009/2010 (SB97Z): Same day Chemotherapy admission/attendance (Day case and Regular Day / Night)]).

A prospective time-and-motion study was conducted in two UK secondary care NHS Trusts to quantify, in terms of time, the secondary care NHS resource use associated with the preparation and administration of XELOX (capecitabine in combination with oxaliplatin) and FOLFOX-6 (5-FU in combination with folinic acid and oxaliplatin) in metastatic colorectal cancer (Millar et al. 2008). The results of the study indicated that dispensing of capecitabine and preparation of oxaliplatin (administered

intravenously) required an average of 12 minutes each. For the base-case it was assumed the time taken to prepare carboplatin and paclitaxel in pharmacy would be the same as that for oxaliplatin as noted in Millar, 2008.

One hour of a hospital pharmacists' time performing patient related activities (accounting for overheads, qualifications, and salary on costs) costs £46 (PSSRU 2010). This equates to a total per cycle administration cost of bevacizumab of £9.20 or a total monthly cost of £12.91.

The total administration and pharmacy costs of cycle one are £280.20 (£271 +£9.20). The total administration and pharmacy costs of subsequent cycles are £137.20 (£128 +£9.20). The total administration and pharmacy costs of month one are £339.43 (£280.20 + 0.431*£137.20) and the total administration and pharmacy costs of subsequent months are £196.43 (£137.20*(365.25/12)/21)

Subsequent cycles of chemotherapy are associated with a tariff of £128 (NHS Reference costs 2009/2010 (SB97Z): Same day Chemotherapy admission/attendance (Day case and Regular Day / Night)), equivalent to £179.81 per month of treatment.

As pharmacy costs are not included within the drug delivery reference costs they were accounted for separately.

Therefore, the total 'per cycle' administration and pharmacy cost of bevacizumab in the first month is £393.19 while subsequent months cost £192.43.

6.5.5.4 Capecitabine administration and pharmacy cost

As capecitabine is an oral therapy it is associated with a pharmacy cost and with a drug delivery cost. For the purposes of the base-case it was assumed that 9 minutes of pharmacy time would be required to dispense capecitabine in each cycle (Millar, Corrie, Hill, & Pulfer 2008). This equates to a 'per cycle' administration cost of capecitabine of £9 or a total monthly cost of £13.04. It was assumed that every cycle a cost of £86 would be necessary to reflect the consultation process by which continuation with treatment is decided.

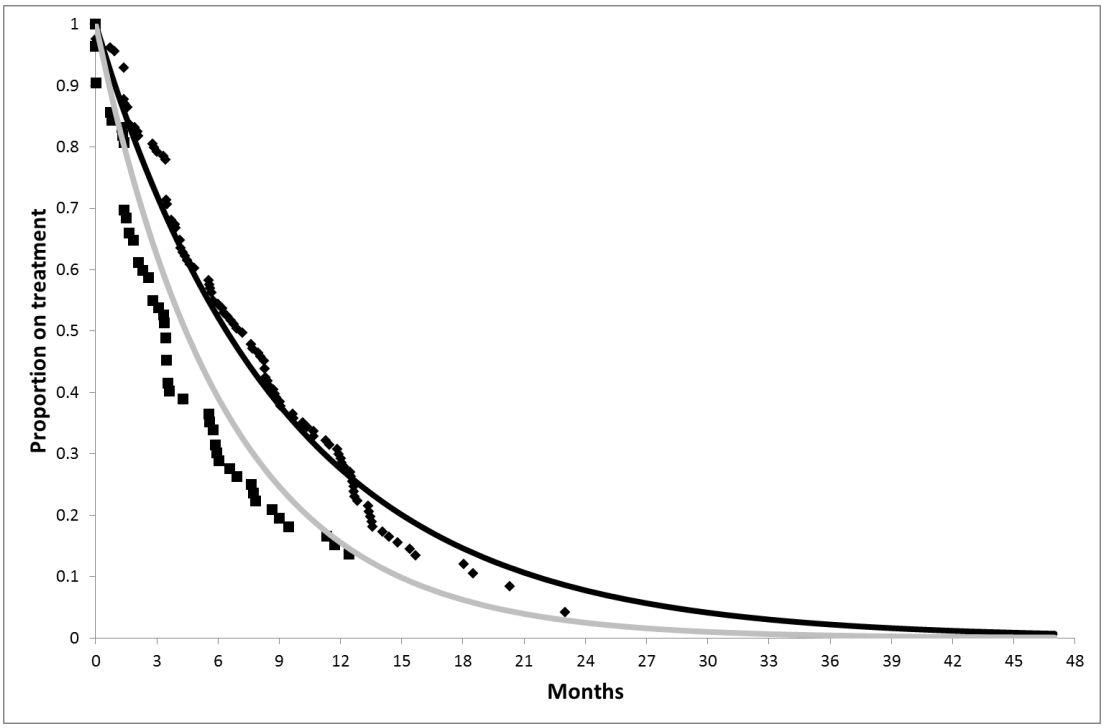
6.5.5.5 Application of aforementioned treatment associated costs

As, in clinical practice, a proportion of patients cease treatment prior to disease progression (due to adverse event, patient preference etc) it is essential to consider the distinction between PFS and treatment cessation when evaluating the real

incremental cost associated with a medical technology. In order to account for this disparity, patient level data on treatment duration was utilised to produce parametrically fitted time to off treatment (TTOT) KM curves that could be applied within the model to determine the proportion of patients still receiving bevacizumab or capecitabine in each month. This fitting was conducted in the same manner as described for PFS and PD.

The time to last treatment dose is calculated as the time from randomization until termination of study treatment due to AE, PD or death. Otherwise, patients are censored at the day of last study treatment. The TTOT Kaplan-Meier survival curve from the RIBBON-1 study was fitted parametrically with a range of different functions (see section 6.3.7). Of the 6 functions fitted, the Gamma and Gompertz models were found to be unstable, hence the Weibull model was chosen as the third best fit was used (Figure 18 and Table 24). The model was half cycle corrected and the time-to-off-treatment was capped at the PFS rate to avoid the impossible situation of more patients being on treatment than being progression free.

Figure 18: Time to off treatment curve: Weibull model (markers; KM data, lines; Weibull estimates.)



Weibull: $S(t) = EXP(-\lambda * t\gamma)$

Table 24: Time to off treatment parameter estimates (Weibull)

Parameter	capecitabine arm	bevacizumab and capecitabine arm
λ	0.159291649	0.110265901
γ	0.989141893	0.989141893

The use of the Weibull function to model TTOT is subject to several caveats. Firstly, although it appears to describe observations in the bevacizumab arm of the trial for the first year of treatment, it tends to over-estimate the probability of remaining on treatment for the second year. Secondly, the probability of remaining on treatment in the capecitabine arm is systematically over-estimated for the first year of the model.

In order to more accurately model the observed time spent on treatment it was assumed that the cumulative hazard plot for the bevacizumab arm of RIBBON-1 was composed of 2 curves as shown in Figure 19. This approach allows for the noticeable change in slope seen at approximately 12 months and does not disregard the behaviour observed for the 40 patients remaining on treatment in the bevacizumab arm at 12 months, representing approximately 25% of the original cohort (N=161).

Figure 19: Cumulative Hazard of treatment duration in RIBBON-1

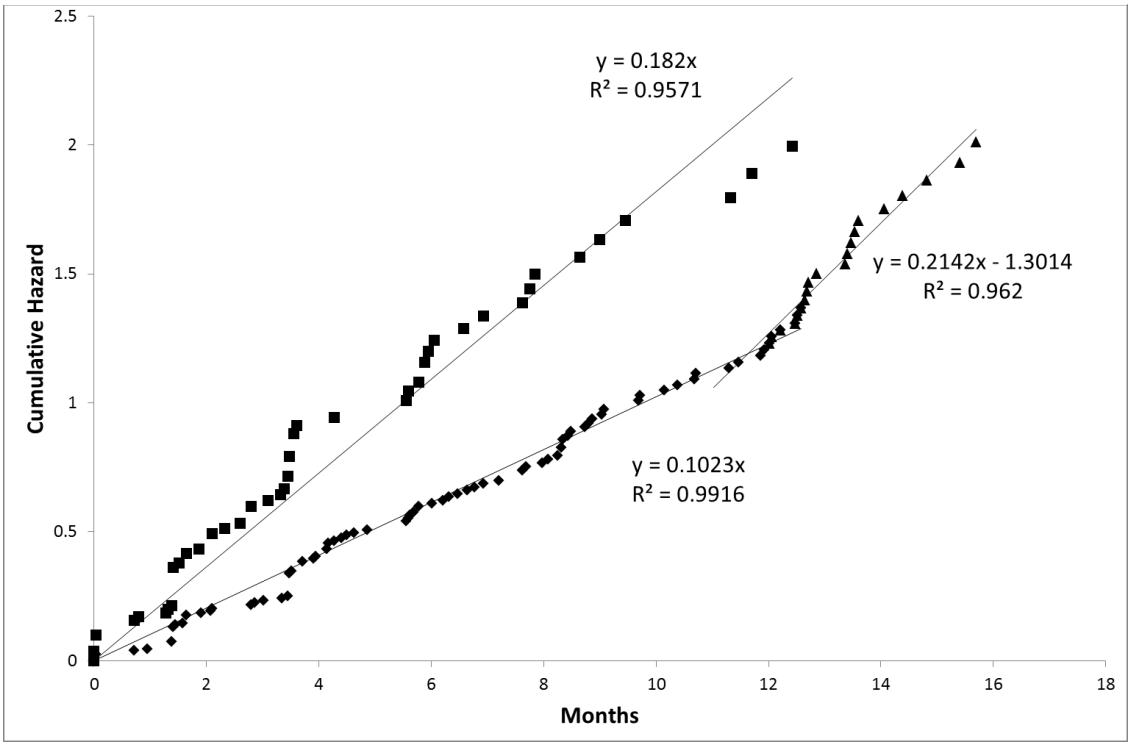
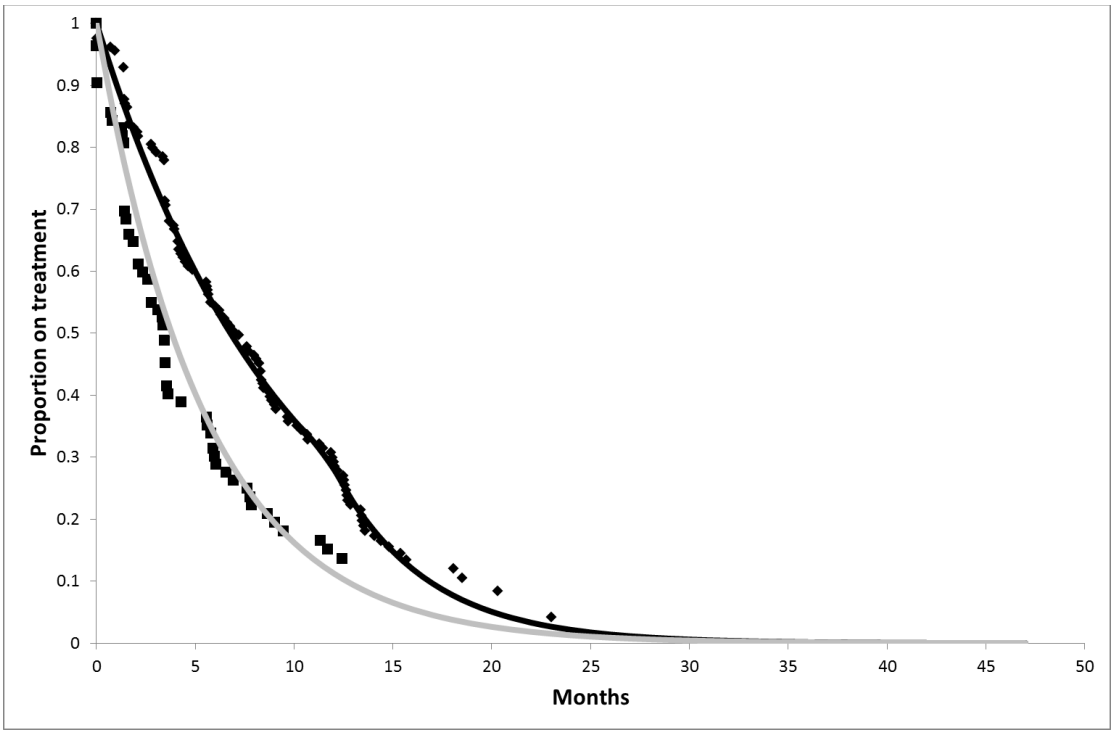


Figure 20: Treatment duration curves calculated from the equations derived in Figure 19



Health-state costs

6.5.6 **Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.**

Table 25: List of health states and associated costs in the economic model

Health states	Items	Frequency	Monthly Cost	Reference in submission
Progression free survival (PFS)	Community Nurse (home visit)	20 mins every 2 weeks	£54.00	Section 6.5.6.1
	GP Contact (surgery visit)	1 every month	£36.00	Section 6.5.6.1
	Clinical Nurse Specialist	1hr every month	£91.00	Section 6.5.6.1
	Outpatient consultant visit	1 every 3 months	£101.00	Section 6.5.6.1
	Response Assessment (CT)	1 every 3 months	£236.78	Section 6.5.6.1
	Total Monthly Cost	-	£181.00	
Progressed Disease (PD)	Community Nurse (home visit)	20 min once a week	£108.00	Section 6.5.6.2
	GP Contact (home visit)	1 visit every 2 weeks	£240.00	Section 6.5.6.2
	Clinical Nurse Specialist	1 hr once a week	£364.00	Section 6.5.6.2
	Therapist	1 hr every 2 weeks	£92.00	Section 6.5.6.2
	Total Monthly Cost	**-**	**£804.00**	

6.5.6.1 Progression Free Survival (PFS)-associated costs

Costs associated with PFS are assumed to be the same as detailed in NICE CG81 (advanced breast cancer clinical guidelines) ‘package 1’ with the addition of an outpatient consultation with an oncologist and a CT scan, assumed to occur every 3 months, to assess response to treatment and/or progression of disease (NICE CG81 2009).

Table 26: Monthly supportive care costs for patients in PFS

Item	Duration of visit (mins)	Frequency (per month)	Unit cost*	Monthly cost	Source
10.1 Community nurse	20	2	£27.00	£54.00	(PSSRU 2010)
10.8 General practitioner	11.7	1	£36.00	£36.00	
10.4 Nurse specialist (community)	60	1	£91.00	£91.00	
Consultant led follow-up attendance, non-admitted, face to face (clinical oncology) service code 800	N/A	0.3	£101.49	£33.83	(Department of Health 2011)
Outpatient CT scan (2 areas with contrast) Reference cost RA12Z	N/A	0.3	£146.16	£48.72	
TOTAL				**£263.55**	

6.5.6.2 Progressed Disease (PD)-associated costs

Costs associated with PD are assumed to be the same as detailed in NICE CG81 (advanced breast cancer clinical guidelines) 'package 2' (NICE CG81 2009).

Table 27: Monthly supportive care costs for patients in PD

Item	Duration of visit (mins)	Frequency (per month)	Unit cost*	Monthly cost
10.1 Community nurse	20	4	£27.00	£108.00
10.4 Nurse specialist (community)	60	4	£91.00	£364.00
10.8 General practitioner	23.4	2	£120.00	£240.00
9.2 NHS community occupational therapist	60	2	£46.00	£92.00
TOTAL				**£804.00**

Adverse-event costs

6.5.7 **Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.**

Only those adverse events occurring in greater than 2% of patients at grade 3/4 severity were incorporated into the analysis. Where possible, NHS reference costs were utilised (Department of Health 2011). Where clinical advice indicated that the usual treatment pathway for the adverse event was discontinuation of treatment, it was assumed this had been accounted for elsewhere in the model and no additional costs were accrued. All adverse events were assumed to occur in month 1 for both BEV/CAP and CAP and so were not discounted.

Table 28: List of adverse events and summary of costs included in the economic model (Grade 3/4 and at >2% incidence rate in either arm only)

Adverse events	% of patients in X arm experiencing	% of patients in BX arm experiencing	Cost per episode	Reference
Deep Vein Thrombosis	0%	3.11%	£389	NHS Reference Costs 2009/2010 (QZ20Z – Non-Elective Short Stay Deep Vein Thrombosis)
Hypertension	0%	8.70%	£455	NHS Reference Costs 2009/2010 (EB041 – Non-Elective Short Stay Hypertension without CC)
Peripheral Sensory Neuropathy	0%	4.35%	N/A	Expert Opinion says treatment is discontinuation of chemotherapy
Diarrhoea*	2.47%	0.62%	N/A	Negligible cost
Palmar-plantar Erythrodysesthesia Syndrome	0%	2.48%	N/A	Expert Opinion says treatment is discontinuation of chemotherapy
Proteinuria	0%	3.73%	N/A	Expert Opinion says treatment is discontinuation of chemotherapy

***Diarrhoea is assumed to be treated with generic rehydration therapies and/or anti-motility agents which have a negligible contribution to total costs.**

Miscellaneous costs

6.5.8 **Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.**

All costs applied within the model are as described in Sections 6.5.1 to 6.5.7.

No terminal phase cost was modelled for either arm. As this cost is normally assumed to occur in the last month of each patient's life (last 2 weeks in the case of CG81 (NICE CG81 2009)) irrespective of the regimen received the inclusion of a terminal cost typically only has minimal (though positive) impact upon the ICER produced (with the change in ICER solely attributable to discounting). Therefore in order to make the model more parsimonious no terminal phase cost was included. In addition as there is no reason to believe duration of 2nd line treatment would be any different for a patient receiving BX first line compared to a patient receiving X first line it was assumed that the cost of 2nd line treatment in each arm would cancel the 2nd line cost in the other arm out and so a 2nd line cost was not implemented within the model.

Sensitivity analysis

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

The 3-state model structure used in this submission has been used in numerous previous NICE metastatic oncology appraisals and is generally accepted as being the appropriate method of modelling mBC, therefore the only structural sensitivity analysis of the model changed the comparator arm to vinorelbine.

Vinorelbine has been assumed to be as effective as capecitabine in a recent clinical guideline (NICE CG81 2009) and therefore in the sensitivity analysis, it was assumed that the comparator arm of the model accrued drug acquisition and administration costs consistent with a vinorelbine monotherapy regimen (Table 29). Vinorelbine is available in an oral as well as an intravenous formulation. Given uncertainty in the

most common route of vinorelbine administration in the NHS, the ICER for both formulations was determined.

Table 29: Calculation of drug acquisition and administration costs for vinorelbine

	Capecitabine base case	Vinorelbine generic (IV)	Navelbine (IV)	Navelbine (oral)
List price				
10mg vial		£5.11 (Commercial Medicines Unit 2011)	£29.75 (Joint Formulary Committee 2011)	
20mg				£43.98 (Joint Formulary Committee 2011)
500mg (120 tab pack)	£265.55 (Joint Formulary Committee 2011)			
Dose (mg/m2)	1000	30	30	60
Frequency (per 3 week cycle)	2 x 14	2	2	3
Average drug cost per month	£312.41	£77.29	£449.99	£1995.70
Cost of administering drug (month 1)	£255.32	£338.94	£338.94	£255.32
Cost of administering drug (subsequent months)	£255.32	£196.09	£196.09	£255.32

6.5.10 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis was carried out on the parameters listed in Table 30 (note: all costs are monthly costs unless otherwise stated). Each cost and utility parameter was varied individually as well as in combination with the others. The parametric functions used to model PFS, PD and TTOT were changed individually to the functions determined by AIC/BIC statistics to be most appropriate. The discount rate for costs and outcomes was varied according to standard methods and the time horizon was increased or decreased by 10 years.

Table 30: Deterministic sensitivity analysis

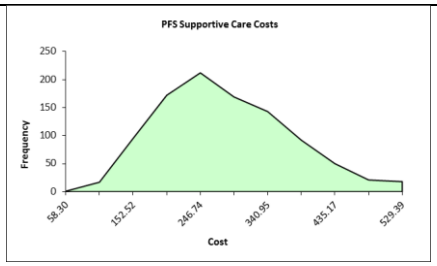
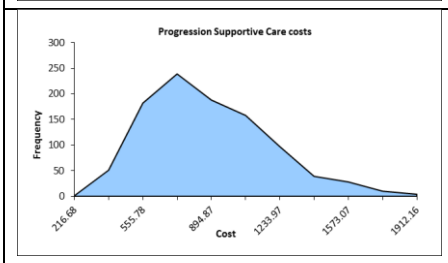
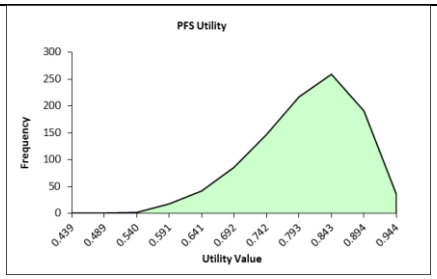
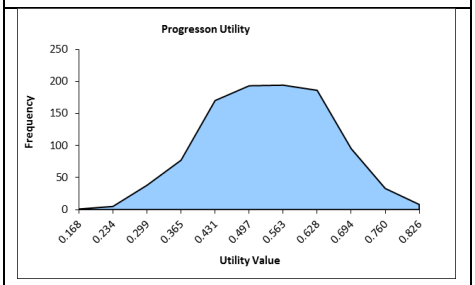
	Base case Value (BCV)	High Value	Low Value
Costs		**(BCVx1.4)**	**(BCVx0.6)**
Bevacizumab administration (1st month)	£338.94	£474.52	£203.36
Bevacizumab administration (other months)	£196.09	£274.52	£117.65
Capecitabine administration in bevacizumab arm	£9.88	£13.83	£5.93
Capecitabine administration in Capecitabine arm	£255.32	£357.45	£153.19
PFS BSC	£263.55	£368.97	£158.13
PD BSC	£804.00	£1,125.60	£482.40
All costs listed above			
Outcomes		**(BCV+0.2)**	**(BCV-0.2)**
PFS utility (Bev)	0.78419	0.98419	0.58419
PFS utility (Cap)	0.77364	0.97364	0.57364
PD utility	0.49612	0.69612	0.29612
All Utilities listed above			
Parametric functions			
PFS parametric fit	Kaplan Meier data with exponential tail	Gompertz	
PD parametric fit		Gompertz	
TTOT parametric fit		Weibull	
Other			
Cost Discount rate	0.035	0.06	0
Health Outcomes Discount rate	0.035	0.06	0
Time horizon	15	25	5

BCV: Base case value

6.5.11 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

A probabilistic sensitivity analysis was undertaken. The distributions utilised are provided in Table 31 below.

Table 31: Probabilistic Sensitivity Analysis

	Distribution	Logic	Graphical
Costs			
PFS BSC and Monitoring	Gamma (7.11, 37.061719)	Gamma is positively constrained (as costs are) and allows the possibility of high 'outlier' values.	
PD BSC	Gamma (7.11, 113.06250)		
Health Outcomes			
PFS Utility	Beta (0.78, 0.000169)	Utility value far enough from 0 to warrant a transformed (1-x) normal function unnecessary. Constrained at the upper end by 1.	
PD Utility	Beta (0.50, 0.000250)		

6.6 Results

Clinical outcomes from the model

6.6.1 **For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.**

Table 32: Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Capecitabine arm		
Progression-free survival	Median = 4.2 months	Median = 4 months
Post-progression survival	N/A	9.79
Overall survival	Median = 15 months	Median = 15 months
Bevacizumab arm		
Progression-free survival	Median = 8.7 months	Median = 8 months
Post-progression survival	N/A	N/A
Overall survival	Median = 24 months	Median = 23 months

6.6.2 **Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.**

Table 33: Markov trace (post-half cycle correction)

	Bevacizumab + Capecitabine			Capecitabine		
Month	**PFS**	**PD**	**Death**	**PFS**	**PD**	**Death**
0	0.9935	0.0039	0.0027	0.9813	0.0147	0.0040
1	0.9477	0.0441	0.0082	0.8808	0.1040	0.0152
2	0.8756	0.1098	0.0146	0.7103	0.2595	0.0302
3	0.8194	0.1582	0.0224	0.5895	0.3637	0.0468
4	0.7356	0.2326	0.0318	0.4912	0.4381	0.0707
5	0.6650	0.2922	0.0428	0.4111	0.4904	0.0985
6	0.6171	0.3254	0.0575	0.3544	0.5177	0.1279

7	0.5723	0.3530	0.0747	0.3039	0.5357	0.1604
8	0.5186	0.3883	0.0931	0.2734	0.5368	0.1898
9	0.4569	0.4268	0.1163	0.2347	0.5426	0.2227
10	0.4297	0.4298	0.1406	0.2112	0.5291	0.2597
11	0.3963	0.4381	0.1655	0.1796	0.5234	0.2970
12	0.3383	0.4703	0.1914	0.1447	0.5136	0.3417
13	0.2719	0.5101	0.2180	0.1239	0.4810	0.3951
14	0.2185	0.5356	0.2459	0.1061	0.4425	0.4513
15	0.1755	0.5517	0.2728	0.0909	0.4043	0.5048
16	0.1411	0.5577	0.3013	0.0779	0.3677	0.5545
17	0.1133	0.5556	0.3310	0.0667	0.3322	0.6012
18	0.0911	0.5483	0.3607	0.0571	0.3002	0.6427
19	0.0732	0.5367	0.3901	0.0489	0.2707	0.6804
20	0.0588	0.5213	0.4199	0.0419	0.2426	0.7155
21	0.0473	0.5033	0.4494	0.0359	0.2174	0.7467
22	0.0380	0.4842	0.4778	0.0307	0.1941	0.7752
23	0.0305	0.4648	0.5047	0.0263	0.1717	0.8019
24	0.0245	0.4452	0.5303	0.0225	0.1516	0.8258
25	0.0197	0.4256	0.5547	0.0193	0.1339	0.8468
26	0.0158	0.4062	0.5780	0.0165	0.1180	0.8655
27	0.0127	0.3871	0.6001	0.0142	0.1038	0.8821
28	0.0102	0.3686	0.6212	0.0121	0.0911	0.8967
29	0.0082	0.3506	0.6412	0.0104	0.0799	0.9097
30	0.0066	0.3332	0.6602	0.0089	0.0700	0.9211
31	0.0053	0.3164	0.6783	0.0076	0.0612	0.9312
32	0.0043	0.3003	0.6954	0.0065	0.0535	0.9400
33	0.0034	0.2849	0.7116	0.0056	0.0467	0.9477
34	0.0028	0.2702	0.7270	0.0048	0.0407	0.9545
35	0.0022	0.2562	0.7416	0.0041	0.0354	0.9605
36	0.0018	0.2428	0.7555	0.0035	0.0308	0.9656
37	0.0014	0.2300	0.7685	0.0030	0.0268	0.9702
38	0.0011	0.2179	0.7810	0.0026	0.0233	0.9741
39	0.0009	0.2064	0.7927	0.0022	0.0202	0.9775
40	0.0007	0.1954	0.8038	0.0019	0.0176	0.9805
41	0.0006	0.1851	0.8143	0.0016	0.0152	0.9831
42	0.0005	0.1752	0.8243	0.0014	0.0132	0.9854
43	0.0004	0.1659	0.8337	0.0012	0.0114	0.9874
44	0.0003	0.1570	0.8427	0.0010	0.0099	0.9891
45	0.0002	0.1486	0.8511	0.0009	0.0086	0.9906
46	0.0002	0.1407	0.8591	0.0007	0.0074	0.9918
47	0.0002	0.1331	0.8667	0.0006	0.0064	0.9929
48	0.0001	0.1260	0.8739	0.0005	0.0055	0.9939
49	0.0001	0.1192	0.8806	0.0005	0.0048	0.9947
50	0.0001	0.1129	0.8871	0.0004	0.0041	0.9955
51	0.0001	0.1068	0.8931	0.0003	0.0036	0.9961
52	0.0001	0.1011	0.8989	0.0003	0.0031	0.9966
53	0.0000	0.0956	0.9043	0.0003	0.0027	0.9971
54	0.0000	0.0905	0.9095	0.0002	0.0023	0.9975
55	0.0000	0.0856	0.9143	0.0002	0.0020	0.9978
56	0.0000	0.0810	0.9189	0.0002	0.0017	0.9981

57	0.0000	0.0767	0.9233	0.0001	0.0015	0.9984
58	0.0000	0.0726	0.9274	0.0001	0.0013	0.9986
59	0.0000	0.0687	0.9313	0.0001	0.0011	0.9988
60	0.0000	0.0650	0.9350	0.0001	0.0009	0.9990
61	0.0000	0.0615	0.9385	0.0001	0.0008	0.9991
62	0.0000	0.0582	0.9418	0.0001	0.0007	0.9992
63	0.0000	0.0550	0.9450	0.0001	0.0006	0.9993
64	0.0000	0.0521	0.9479	0.0000	0.0005	0.9994
65	0.0000	0.0493	0.9507	0.0000	0.0004	0.9995
66	0.0000	0.0466	0.9534	0.0000	0.0004	0.9996
67	0.0000	0.0441	0.9559	0.0000	0.0003	0.9996
68	0.0000	0.0417	0.9583	0.0000	0.0003	0.9997
69	0.0000	0.0395	0.9605	0.0000	0.0002	0.9997
70	0.0000	0.0374	0.9626	0.0000	0.0002	0.9998
71	0.0000	0.0354	0.9646	0.0000	0.0002	0.9998
72	0.0000	0.0335	0.9665	0.0000	0.0002	0.9998
73	0.0000	0.0317	0.9683	0.0000	0.0001	0.9999
74	0.0000	0.0300	0.9700	0.0000	0.0001	0.9999
75	0.0000	0.0283	0.9717	0.0000	0.0001	0.9999
76	0.0000	0.0268	0.9732	0.0000	0.0001	0.9999
77	0.0000	0.0254	0.9746	0.0000	0.0001	0.9999
78	0.0000	0.0240	0.9760	0.0000	0.0001	0.9999
79	0.0000	0.0227	0.9773	0.0000	0.0000	0.9999
80	0.0000	0.0215	0.9785	0.0000	0.0000	1.0000
81	0.0000	0.0203	0.9797	0.0000	0.0000	1.0000
82	0.0000	0.0192	0.9808	0.0000	0.0000	1.0000
83	0.0000	0.0182	0.9818	0.0000	0.0000	1.0000
84	0.0000	0.0172	0.9828	0.0000	0.0000	1.0000
85	0.0000	0.0163	0.9837	0.0000	0.0000	1.0000
86	0.0000	0.0154	0.9846	0.0000	0.0000	1.0000
87	0.0000	0.0146	0.9854	0.0000	0.0000	1.0000
88	0.0000	0.0138	0.9862	0.0000	0.0000	1.0000
89	0.0000	0.0131	0.9869	0.0000	0.0000	1.0000
90	0.0000	0.0124	0.9876	0.0000	0.0000	1.0000
91	0.0000	0.0117	0.9883	0.0000	0.0000	1.0000
92	0.0000	0.0111	0.9889	0.0000	0.0000	1.0000
93	0.0000	0.0105	0.9895	0.0000	0.0000	1.0000
94	0.0000	0.0099	0.9901	0.0000	0.0000	1.0000
95	0.0000	0.0094	0.9906	0.0000	0.0000	1.0000
96	0.0000	0.0089	0.9911	0.0000	0.0000	1.0000
97	0.0000	0.0084	0.9916	0.0000	0.0000	1.0000
98	0.0000	0.0079	0.9921	0.0000	0.0000	1.0000
99	0.0000	0.0075	0.9925	0.0000	0.0000	1.0000
100	0.0000	0.0071	0.9929	0.0000	0.0000	1.0000
101	0.0000	0.0067	0.9933	0.0000	0.0000	1.0000
102	0.0000	0.0064	0.9936	0.0000	0.0000	1.0000
103	0.0000	0.0060	0.9940	0.0000	0.0000	1.0000
104	0.0000	0.0057	0.9943	0.0000	0.0000	1.0000
105	0.0000	0.0054	0.9946	0.0000	0.0000	1.0000
106	0.0000	0.0051	0.9949	0.0000	0.0000	1.0000

107	0.0000	0.0048	0.9952	0.0000	0.0000	1.0000
108	0.0000	0.0046	0.9954	0.0000	0.0000	1.0000
109	0.0000	0.0043	0.9957	0.0000	0.0000	1.0000
110	0.0000	0.0041	0.9959	0.0000	0.0000	1.0000
111	0.0000	0.0039	0.9961	0.0000	0.0000	1.0000
112	0.0000	0.0037	0.9963	0.0000	0.0000	1.0000
113	0.0000	0.0035	0.9965	0.0000	0.0000	1.0000
114	0.0000	0.0033	0.9967	0.0000	0.0000	1.0000
115	0.0000	0.0031	0.9969	0.0000	0.0000	1.0000
116	0.0000	0.0029	0.9971	0.0000	0.0000	1.0000
117	0.0000	0.0028	0.9972	0.0000	0.0000	1.0000
118	0.0000	0.0026	0.9974	0.0000	0.0000	1.0000
119	0.0000	0.0025	0.9975	0.0000	0.0000	1.0000
120	0.0000	0.0024	0.9976	0.0000	0.0000	1.0000
121	0.0000	0.0022	0.9978	0.0000	0.0000	1.0000
122	0.0000	0.0021	0.9979	0.0000	0.0000	1.0000
123	0.0000	0.0020	0.9980	0.0000	0.0000	1.0000
124	0.0000	0.0019	0.9981	0.0000	0.0000	1.0000
125	0.0000	0.0018	0.9982	0.0000	0.0000	1.0000
126	0.0000	0.0017	0.9983	0.0000	0.0000	1.0000
127	0.0000	0.0016	0.9984	0.0000	0.0000	1.0000
128	0.0000	0.0015	0.9985	0.0000	0.0000	1.0000
129	0.0000	0.0014	0.9986	0.0000	0.0000	1.0000
130	0.0000	0.0014	0.9986	0.0000	0.0000	1.0000
131	0.0000	0.0013	0.9987	0.0000	0.0000	1.0000
132	0.0000	0.0012	0.9988	0.0000	0.0000	1.0000
133	0.0000	0.0011	0.9989	0.0000	0.0000	1.0000
134	0.0000	0.0011	0.9989	0.0000	0.0000	1.0000
135	0.0000	0.0010	0.9990	0.0000	0.0000	1.0000
136	0.0000	0.0010	0.9990	0.0000	0.0000	1.0000
137	0.0000	0.0009	0.9991	0.0000	0.0000	1.0000
138	0.0000	0.0009	0.9991	0.0000	0.0000	1.0000
139	0.0000	0.0008	0.9992	0.0000	0.0000	1.0000
140	0.0000	0.0008	0.9992	0.0000	0.0000	1.0000
141	0.0000	0.0007	0.9993	0.0000	0.0000	1.0000
142	0.0000	0.0007	0.9993	0.0000	0.0000	1.0000
143	0.0000	0.0007	0.9993	0.0000	0.0000	1.0000
144	0.0000	0.0006	0.9994	0.0000	0.0000	1.0000
145	0.0000	0.0006	0.9994	0.0000	0.0000	1.0000
146	0.0000	0.0006	0.9994	0.0000	0.0000	1.0000
147	0.0000	0.0005	0.9995	0.0000	0.0000	1.0000
148	0.0000	0.0005	0.9995	0.0000	0.0000	1.0000
149	0.0000	0.0005	0.9995	0.0000	0.0000	1.0000
150	0.0000	0.0004	0.9996	0.0000	0.0000	1.0000
151	0.0000	0.0004	0.9996	0.0000	0.0000	1.0000
152	0.0000	0.0004	0.9996	0.0000	0.0000	1.0000
153	0.0000	0.0004	0.9996	0.0000	0.0000	1.0000
154	0.0000	0.0004	0.9996	0.0000	0.0000	1.0000
155	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000
156	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000

157	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000
158	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000
159	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000
160	0.0000	0.0003	0.9997	0.0000	0.0000	1.0000
161	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
162	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
163	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
164	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
165	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
166	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
167	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
168	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
169	0.0000	0.0002	0.9998	0.0000	0.0000	1.0000
170	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
171	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
172	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
173	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
174	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
175	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
176	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
177	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
178	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
179	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
180	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
181	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
182	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
183	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
184	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
185	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
186	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
187	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
188	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
189	0.0000	0.0001	0.9999	0.0000	0.0000	1.0000
190	0.0000	0.0000	1.0000	0.0000	0.0000	1.0000
191	0.0000	0.0000	1.0000	0.0000	0.0000	1.0000

6.6.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Table 34: QALY accumulation 'trace' (with discounting and half cycle correction)

	Bevacizumab + Capecitabine			Capecitabine		
Month	**PFS**	**PD**	**Total**	**PFS**	**PD**	**Total**
0	0.779058	0.001929	0.780987	0.769491	0.007315	0.776805
1	0.743181	0.021857	0.765038	0.690718	0.05161	0.742328
2	0.68664	0.054456	0.741096	0.557013	0.12875	0.685764
3	0.64253	0.078491	0.721021	0.462282	0.180463	0.642745
4	0.576853	0.115378	0.692231	0.385157	0.217354	0.602511

5	0.521489	0.144948	0.666437	0.322382	0.243318	0.5657
6	0.483887	0.161449	0.645336	0.277879	0.256864	0.534743
7	0.448794	0.175106	0.6239	0.238317	0.265772	0.504089
8	0.406683	0.192635	0.599319	0.214399	0.266306	0.480705
9	0.358259	0.211767	0.570026	0.184011	0.269201	0.453212
10	0.336929	0.213216	0.550145	0.165622	0.26252	0.428142
11	0.3108	0.217368	0.528169	0.140865	0.259669	0.400534
12	0.256332	0.225452	0.481783	0.109618	0.246213	0.355831
13	0.205979	0.244516	0.450495	0.093888	0.230567	0.324455
14	0.165517	0.256735	0.422252	0.079333	0.212131	0.291464
15	0.133003	0.264455	0.397458	0.067949	0.193789	0.261737
16	0.106876	0.267315	0.374191	0.058198	0.17623	0.234428
17	0.085882	0.266341	0.352222	0.049847	0.159218	0.209065
18	0.069011	0.262802	0.331814	0.042694	0.143883	0.186577
19	0.055455	0.257247	0.312702	0.036567	0.129734	0.166301
20	0.044562	0.249867	0.294428	0.03132	0.11628	0.1476
21	0.035808	0.241251	0.277059	0.026826	0.104225	0.131051
22	0.028774	0.232104	0.260878	0.022976	0.093019	0.115995
23	0.023122	0.222775	0.245897	0.019679	0.082316	0.101995
24	0.017951	0.206172	0.224123	0.016285	0.070231	0.086516
25	0.014425	0.197096	0.211522	0.013948	0.061999	0.075947
26	0.011591	0.188114	0.199705	0.011947	0.054628	0.066575
27	0.009314	0.179295	0.18861	0.010232	0.048051	0.058283
28	0.007485	0.170696	0.178181	0.008764	0.042198	0.050962
29	0.006014	0.162354	0.168368	0.007506	0.037005	0.044511
30	0.004833	0.154295	0.159128	0.006429	0.032407	0.038837
31	0.003884	0.146537	0.150421	0.005507	0.028346	0.033853
32	0.003121	0.13909	0.142211	0.004716	0.024765	0.029482
33	0.002508	0.131958	0.134465	0.00404	0.021614	0.025654
34	0.002015	0.12514	0.127155	0.00346	0.018845	0.022305
35	0.001619	0.118634	0.120253	0.002963	0.016416	0.019379
36	0.001257	0.108632	0.109889	0.002452	0.013804	0.016257
37	0.00101	0.102929	0.103939	0.0021	0.012005	0.014106
38	0.000812	0.097505	0.098316	0.001799	0.010432	0.012231
39	0.000652	0.09235	0.093003	0.001541	0.009059	0.0106
40	0.000524	0.087455	0.087979	0.00132	0.007862	0.009182
41	0.000421	0.082809	0.08323	0.00113	0.006819	0.007949
42	0.000338	0.078401	0.07874	0.000968	0.00591	0.006878
43	0.000272	0.074221	0.074493	0.000829	0.00512	0.005949
44	0.000219	0.070259	0.070478	0.00071	0.004433	0.005143
45	0.000176	0.066504	0.066679	0.000608	0.003837	0.004445
46	0.000141	0.062946	0.063087	0.000521	0.003319	0.00384
47	0.000113	0.059575	0.059689	0.000446	0.00287	0.003316
48	8.8E-05	0.054476	0.054564	0.000369	0.002396	0.002766
49	7.07E-05	0.051555	0.051626	0.000316	0.00207	0.002387
50	5.69E-05	0.04879	0.048846	0.000271	0.001788	0.002059
51	4.57E-05	0.046171	0.046217	0.000232	0.001544	0.001776
52	3.67E-05	0.043692	0.043729	0.000199	0.001332	0.001531
53	2.95E-05	0.041346	0.041375	0.00017	0.001149	0.00132
54	2.37E-05	0.039125	0.039149	0.000146	0.000991	0.001137

55	1.9E-05	0.037023	0.037042	0.000125	0.000855	0.00098
56	1.53E-05	0.035033	0.035048	0.000107	0.000737	0.000844
57	1.23E-05	0.03315	0.033162	9.16E-05	0.000635	0.000727
58	9.88E-06	0.031368	0.031378	7.85E-05	0.000547	0.000626
59	7.94E-06	0.029681	0.029689	6.72E-05	0.000471	0.000538
60	6.17E-06	0.027136	0.027142	5.56E-05	0.000392	0.000448
61	4.95E-06	0.025677	0.025682	4.76E-05	0.000337	0.000385
62	3.98E-06	0.024296	0.0243	4.08E-05	0.00029	0.000331
63	3.2E-06	0.022989	0.022992	3.49E-05	0.00025	0.000285
64	2.57E-06	0.021753	0.021755	2.99E-05	0.000215	0.000245
65	2.07E-06	0.020583	0.020585	2.56E-05	0.000185	0.00021
66	1.66E-06	0.019476	0.019477	2.2E-05	0.000159	0.000181
67	1.33E-06	0.018428	0.018429	1.88E-05	0.000136	0.000155
68	1.07E-06	0.017437	0.017438	1.61E-05	0.000117	0.000133
69	8.61E-07	0.016499	0.0165	1.38E-05	0.0001	0.000114
70	6.92E-07	0.015611	0.015612	1.18E-05	8.61E-05	9.79E-05
71	5.56E-07	0.014771	0.014772	1.01E-05	7.38E-05	8.39E-05
72	4.32E-07	0.013504	0.013505	8.37E-06	6.1E-05	6.94E-05
73	3.47E-07	0.012778	0.012778	7.17E-06	5.23E-05	5.94E-05
74	2.79E-07	0.01209	0.01209	6.14E-06	4.47E-05	5.08E-05
75	2.24E-07	0.01144	0.01144	5.26E-06	3.82E-05	4.35E-05
76	1.8E-07	0.010824	0.010825	4.51E-06	3.26E-05	3.71E-05
77	1.45E-07	0.010242	0.010242	3.86E-06	2.78E-05	3.17E-05
78	1.16E-07	0.009691	0.009691	3.31E-06	2.37E-05	2.7E-05
79	9.34E-08	0.00917	0.00917	2.83E-06	2.02E-05	2.3E-05
80	7.51E-08	0.008676	0.008676	2.43E-06	1.71E-05	1.95E-05
81	6.03E-08	0.00821	0.00821	2.08E-06	1.45E-05	1.66E-05
82	4.85E-08	0.007768	0.007768	1.78E-06	1.22E-05	1.4E-05
83	3.89E-08	0.00735	0.00735	1.52E-06	1.03E-05	1.18E-05
84	3.02E-08	0.006719	0.006719	1.26E-06	8.37E-06	9.63E-06
85	2.43E-08	0.006358	0.006358	1.08E-06	7E-06	8.08E-06
86	1.95E-08	0.006016	0.006016	9.25E-07	5.82E-06	6.75E-06
87	1.57E-08	0.005692	0.005692	7.92E-07	4.81E-06	5.6E-06
88	1.26E-08	0.005386	0.005386	6.79E-07	3.94E-06	4.62E-06
89	1.01E-08	0.005096	0.005096	5.81E-07	3.19E-06	3.77E-06
90	8.14E-09	0.004822	0.004822	4.98E-07	2.55E-06	3.05E-06
91	6.54E-09	0.004562	0.004562	4.26E-07	2E-06	2.43E-06
92	5.26E-09	0.004317	0.004317	3.65E-07	1.53E-06	1.9E-06
93	4.22E-09	0.004085	0.004085	3.13E-07	1.13E-06	1.44E-06
94	3.39E-09	0.003865	0.003865	2.68E-07	7.81E-07	1.05E-06
95	2.73E-09	0.003657	0.003657	2.29E-07	4.83E-07	7.12E-07
96	2.12E-09	0.003343	0.003343	1.9E-07	2.2E-07	4.1E-07
97	1.7E-09	0.003163	0.003163	1.63E-07	8.01E-09	1.71E-07
98	1.37E-09	0.002993	0.002993	1.39E-07	-1.7E-07	-3.4E-08
99	1.1E-09	0.002832	0.002832	1.19E-07	-3.3E-07	-2.1E-07
100	8.83E-10	0.00268	0.00268	1.02E-07	-4.6E-07	-3.6E-07
101	7.1E-10	0.002536	0.002536	8.75E-08	-5.8E-07	-4.9E-07
102	5.7E-10	0.002399	0.002399	7.5E-08	-6.8E-07	-6E-07
103	4.58E-10	0.00227	0.00227	6.42E-08	-7.6E-07	-7E-07
104	3.68E-10	0.002148	0.002148	5.5E-08	-8.3E-07	-7.8E-07

105	2.96E-10	0.002032	0.002032	4.71E-08	-8.9E-07	-8.5E-07
106	2.38E-10	0.001923	0.001923	4.03E-08	-9.5E-07	-9.1E-07
107	1.91E-10	0.001819	0.001819	3.46E-08	-9.9E-07	-9.6E-07
108	1.48E-10	0.001663	0.001663	2.86E-08	-1E-06	-9.7E-07
109	1.19E-10	0.001574	0.001574	2.45E-08	-1E-06	-1E-06
110	9.58E-11	0.001489	0.001489	2.1E-08	-1.1E-06	-1E-06
111	7.7E-11	0.001409	0.001409	1.8E-08	-1.1E-06	-1.1E-06
112	6.18E-11	0.001333	0.001333	1.54E-08	-1.1E-06	-1.1E-06
113	4.97E-11	0.001261	0.001261	1.32E-08	-1.1E-06	-1.1E-06
114	3.99E-11	0.001194	0.001194	1.13E-08	-1.1E-06	-1.1E-06
115	3.21E-11	0.001129	0.001129	9.67E-09	-1.1E-06	-1.1E-06
116	2.58E-11	0.001069	0.001069	8.28E-09	-1.2E-06	-1.1E-06
117	2.07E-11	0.001011	0.001011	7.09E-09	-1.2E-06	-1.2E-06
118	1.66E-11	0.000957	0.000957	6.08E-09	-1.2E-06	-1.2E-06
119	1.34E-11	0.000905	0.000905	5.2E-09	-1.2E-06	-1.2E-06
120	1.04E-11	0.000827	0.000827	4.31E-09	-1.1E-06	-1.1E-06
121	8.35E-12	0.000783	0.000783	3.69E-09	-1.2E-06	-1.1E-06
122	6.71E-12	0.000741	0.000741	3.16E-09	-1.2E-06	-1.2E-06
123	5.39E-12	0.000701	0.000701	2.71E-09	-1.2E-06	-1.2E-06
124	4.33E-12	0.000663	0.000663	2.32E-09	-1.2E-06	-1.2E-06
125	3.48E-12	0.000628	0.000628	1.99E-09	-1.2E-06	-1.2E-06
126	2.8E-12	0.000594	0.000594	1.7E-09	-1.2E-06	-1.2E-06
127	2.25E-12	0.000562	0.000562	1.46E-09	-1.2E-06	-1.2E-06
128	1.81E-12	0.000532	0.000532	1.25E-09	-1.2E-06	-1.2E-06
129	1.45E-12	0.000503	0.000503	1.07E-09	-1.2E-06	-1.2E-06
130	1.17E-12	0.000476	0.000476	9.15E-10	-1.2E-06	-1.2E-06
131	9.37E-13	0.00045	0.00045	7.84E-10	-1.2E-06	-1.2E-06
132	7.27E-13	0.000412	0.000412	6.49E-10	-1.1E-06	-1.1E-06
133	5.85E-13	0.000389	0.000389	5.55E-10	-1.1E-06	-1.1E-06
134	4.7E-13	0.000368	0.000368	4.76E-10	-1.1E-06	-1.1E-06
135	3.77E-13	0.000349	0.000349	4.07E-10	-1.1E-06	-1.1E-06
136	3.03E-13	0.00033	0.00033	3.49E-10	-1.1E-06	-1.1E-06
137	2.44E-13	0.000312	0.000312	2.99E-10	-1.1E-06	-1.1E-06
138	1.96E-13	0.000295	0.000295	2.56E-10	-1.1E-06	-1.1E-06
139	1.57E-13	0.000279	0.000279	2.19E-10	-1.1E-06	-1.1E-06
140	1.26E-13	0.000264	0.000264	1.88E-10	-1.1E-06	-1.1E-06
141	1.02E-13	0.00025	0.00025	1.61E-10	-1.1E-06	-1.1E-06
142	8.17E-14	0.000237	0.000237	1.38E-10	-1.1E-06	-1.1E-06
143	6.56E-14	0.000224	0.000224	1.18E-10	-1.1E-06	-1.1E-06
144	5.09E-14	0.000205	0.000205	9.77E-11	-1.1E-06	-1.1E-06
145	4.09E-14	0.000194	0.000194	8.36E-11	-1.1E-06	-1.1E-06
146	3.29E-14	0.000183	0.000183	7.16E-11	-1.1E-06	-1.1E-06
147	2.64E-14	0.000173	0.000173	6.14E-11	-1.1E-06	-1.1E-06
148	2.12E-14	0.000164	0.000164	5.26E-11	-1.1E-06	-1.1E-06
149	1.71E-14	0.000155	0.000155	4.5E-11	-1.1E-06	-1.1E-06
150	1.37E-14	0.000147	0.000147	3.86E-11	-1.1E-06	-1.1E-06
151	1.1E-14	0.000139	0.000139	3.3E-11	-1.1E-06	-1.1E-06
152	8.86E-15	0.000131	0.000131	2.83E-11	-1.1E-06	-1.1E-06
153	7.12E-15	0.000124	0.000124	2.42E-11	-1.1E-06	-1.1E-06
154	5.72E-15	0.000118	0.000118	2.07E-11	-1.1E-06	-1.1E-06

155	4.6E-15	0.000111	0.000111	1.78E-11	-1.1E-06	-1.1E-06
156	3.57E-15	0.000102	0.000102	1.47E-11	-1.1E-06	-1.1E-06
157	2.87E-15	9.62E-05	9.62E-05	1.26E-11	-1.1E-06	-1.1E-06
158	2.3E-15	9.1E-05	9.1E-05	1.08E-11	-1.1E-06	-1.1E-06
159	1.85E-15	8.61E-05	8.61E-05	9.24E-12	-1.1E-06	-1.1E-06
160	1.49E-15	8.14E-05	8.14E-05	7.91E-12	-1.1E-06	-1.1E-06
161	1.2E-15	7.71E-05	7.71E-05	6.78E-12	-1.1E-06	-1.1E-06
162	9.6E-16	7.29E-05	7.29E-05	5.81E-12	-1.1E-06	-1.1E-06
163	7.72E-16	6.9E-05	6.9E-05	4.97E-12	-1.1E-06	-1.1E-06
164	6.2E-16	6.52E-05	6.52E-05	4.26E-12	-1.1E-06	-1.1E-06
165	4.98E-16	6.17E-05	6.17E-05	3.65E-12	-1.1E-06	-1.1E-06
166	4E-16	5.84E-05	5.84E-05	3.12E-12	-1.1E-06	-1.1E-06
167	3.22E-16	5.52E-05	5.52E-05	2.68E-12	-1.1E-06	-1.1E-06
168	2.5E-16	5.05E-05	5.05E-05	2.21E-12	-1E-06	-1E-06
169	2.01E-16	4.77E-05	4.77E-05	1.9E-12	-1E-06	-1E-06
170	1.61E-16	4.51E-05	4.51E-05	1.62E-12	-1E-06	-1E-06
171	1.3E-16	4.27E-05	4.27E-05	1.39E-12	-1E-06	-1E-06
172	1.04E-16	4.04E-05	4.04E-05	1.19E-12	-1E-06	-1E-06
173	8.37E-17	3.82E-05	3.82E-05	1.02E-12	-1E-06	-1E-06
174	6.73E-17	3.61E-05	3.61E-05	8.74E-13	-1E-06	-1E-06
175	5.41E-17	3.42E-05	3.42E-05	7.49E-13	-1E-06	-1E-06
176	4.34E-17	3.23E-05	3.23E-05	6.41E-13	-1E-06	-1E-06
177	3.49E-17	3.06E-05	3.06E-05	5.49E-13	-1E-06	-1E-06
178	2.8E-17	2.89E-05	2.89E-05	4.71E-13	-1E-06	-1E-06
179	2.25E-17	2.73E-05	2.73E-05	4.03E-13	-1E-06	-1E-06
180	1.75E-17	2.5E-05	2.5E-05	3.34E-13	-1E-06	-1E-06
181	1.41E-17	2.36E-05	2.36E-05	2.86E-13	-1E-06	-1E-06
182	1.13E-17	2.23E-05	2.23E-05	2.45E-13	-1E-06	-1E-06
183	9.08E-18	2.11E-05	2.11E-05	2.1E-13	-1E-06	-1E-06
184	7.3E-18	2E-05	2E-05	1.79E-13	-1E-06	-1E-06
185	5.86E-18	1.89E-05	1.89E-05	1.54E-13	-1E-06	-1E-06
186	4.71E-18	1.78E-05	1.78E-05	1.32E-13	-1E-06	-1E-06
187	3.79E-18	1.69E-05	1.69E-05	1.13E-13	-1E-06	-1E-06
188	3.04E-18	1.59E-05	1.59E-05	9.66E-14	-1E-06	-1E-06
189	2.44E-18	1.51E-05	1.51E-05	8.27E-14	-1E-06	-1E-06
190	1.96E-18	1.42E-05	1.42E-05	7.09E-14	-1E-06	-1E-06
191	1.58E-18	1.35E-05	1.35E-05	6.07E-14	-1E-06	-1E-06

6.6.4 **Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results**

Table 35: Model outputs by clinical outcomes

Comparator	Outcome	LY	QALY	Cost (£)
Bevacizumab + capecitabine	PFS	0.8073	0.6330	37,866
	PD	1.4211	0.7050	13,711
	Overall survival	2.2283	1.3381	51,645
Capecitabine	PFS	0.5491	0.4300	4,852
	PD	0.8156	0.4047	7,869
	Overall survival	1.3648	0.8346	12,721
	LY, life years; QALY, quality-adjusted life year			

6.6.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 36: Summary of QALY gain by health state

Health state	QALY intervention (Bev)	QALY comparator (Cap)	Increment	% absolute increment
PFS	0.6330	0.4300	0.2031	40.3%
PD	0.7050	0.4047	0.3004	59.7%
Total	**1.3381**	**0.8346**	**0.5034**	**100%**

Table 37: Summary of costs by health state

Health state	Cost intervention (Bev)	Cost comparator (Cap)	Increment	% absolute increment
PFS	£37,866	£4,852	£33,015	85.0%
PD	£13,711	£7,869	£5,841	15.0%
Total	£51,577	£12,721	£38,856	100%

Table 38: Summary of predicted resource use by category of cost

Item	Cost intervention (Bev)	Cost comparator (Cap)	Increment	Absolute increment	% absolute increment
Mean total treatment cost (Bev)	30,840	0	30,840	30,840	79.2%
Administration cost (Bev)	1,779	0	1,779	1,779	4.6%
Mean total treatment cost (Cap)	2,612	1,714	898	898	2.3%
Administration cost (Cap)	83	1,401	-1,318	1,318	3.4%
Mean Supportive Care Cost of PFS	2,553	1,737	816	816	2.1%
Mean Supportive Care Cost of PD	13,711	7,869	5,841	5,841	15.0%
Cost of AE's	68	0	68	68	0.2%
Total	**51,645**	**12,721**	**38,924**	**38,924**	**100%**

Base-case analysis

6.6.6 **Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.**

Table 39: Base-case results

Technologies	Total costs (£)	Total Life Years	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus incremental LYG	ICER (£) incremental (QALYs)
Capecitabine	12,721	1.3648	0.8346					
Bevacizumab + capecitabine	51,645	2.2283	1.3381	38,924	0.8636	0.5034	45,073	77,318
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses

6.6.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

The results presented in Table 40 demonstrate that the ICER for the addition of bevacizumab to capecitabine in these patients is most sensitive to assumptions concerning the costs and utilities associated with progressed disease.

Table 40: Deterministic univariate sensitivity analysis results

	Base case Value	High Value	Low Value	High Result (ICER)	Low Result (ICER)
Costs				**£77,318**	
Bevacizumab administration (1st month)	£338.94	£474.52	£203.36	£77,581	£77,055
Bevacizumab administration (other months)	£196.09	£274.52	£117.65	£78,468	£76,168
Capecitabine administration in bevacizumab arm	£9.88	£13.83	£5.93	£77,384	£77,252
Capecitabine administration in Capecitabine arm	£255.32	£357.45	£153.19	£76,205	£78,431
PFS BSC	£263.55	£368.97	£158.13	£77,967	£76,669
PD BSC	£804.00	£1,125.60	£482.40	£81,959	£72,677
All costs				£82,974	£71,662
Outcomes					
PFS utility (Bev)	0.78419	0.98419	0.58419	£68,665	£88,466
PFS utility (Cap)	0.77364	0.97364	0.57364	£79,175	£75,546
PD utility	0.49612	0.69612	0.29612	£62,327	£101,804
All Utilities above				£57,568	£117,698
PFS parametric fit	KM	Gompertz			£74,879
PD parametric fit	KM	Gompertz			£110,092
TTOT parametric fit	KM	Weibull			£83,030
Other					
Cost Discount rate	0.035	0.06	0	£76,209	£79,064
Health Outcomes Discount rate	0.035	0.06	0	£81,020	£72,068
Time horizon	15	10	5	£77,457	£82,351

6.6.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The results of the PSA suggest that the addition of bevacizumab to capecitabine would never (0% probability) be considered cost-effective at a willingness-to-pay of £30,000 or £50,000 per QALY gained (Figure 21 and Figure 22).

Figure 21: Cost-effectiveness plane for the addition of bevacizumab to capecitabine in mBC

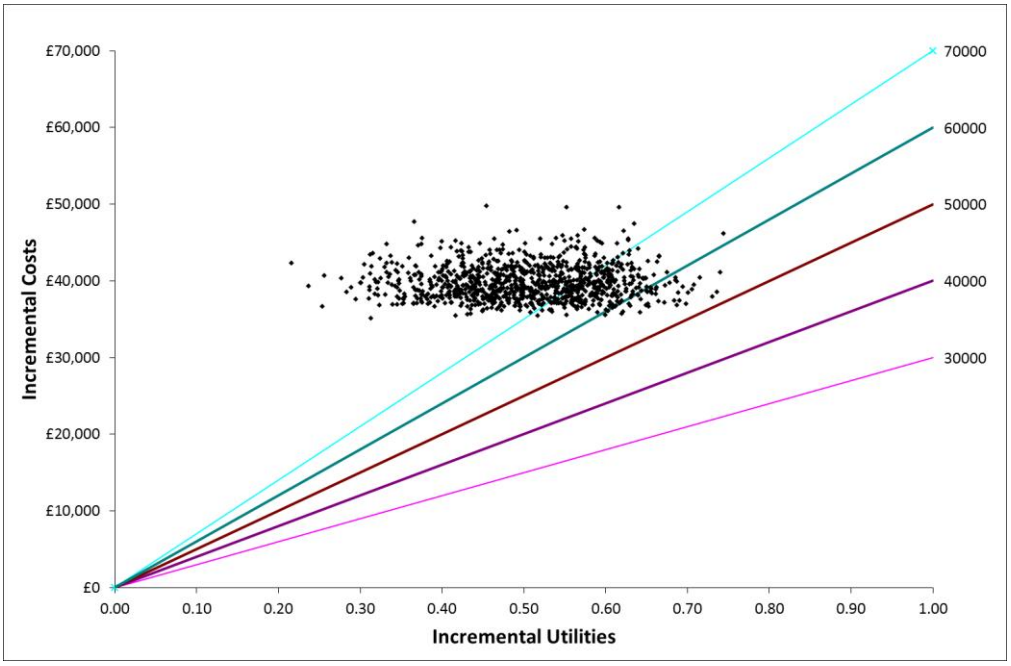
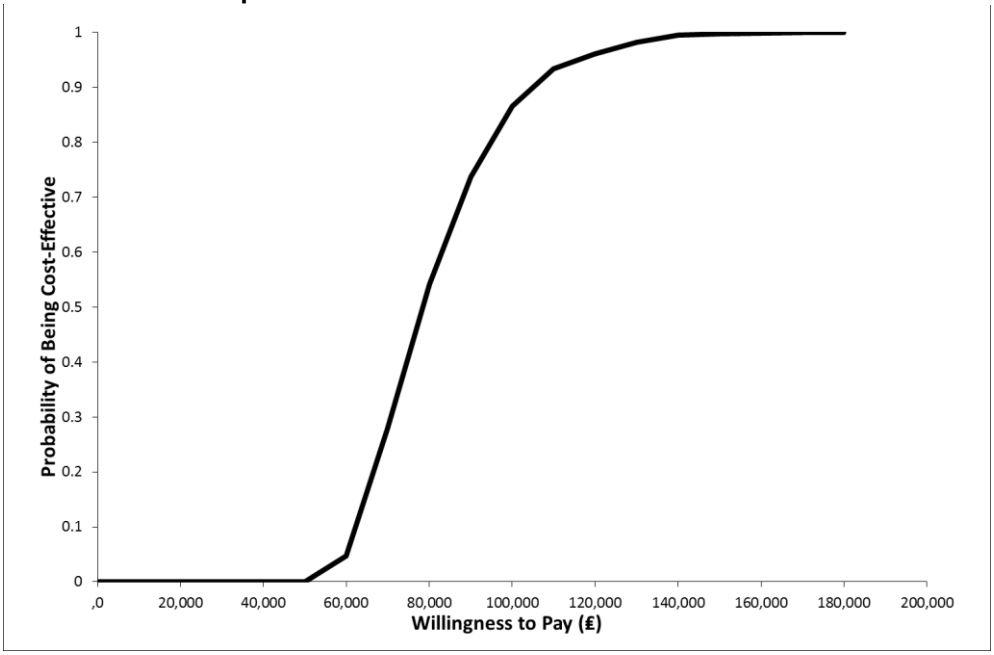


Figure 22: Cost-effectiveness acceptability curve for the addition of bevacizumab to capecitabine in mBC



6.6.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Utility estimates

A recent systematic review of utility studies in breast cancer provides alternative estimates for the HRQoL of patients in this model and these were used in a sensitivity analysis.

Table 41: Alternative sources of utilities in mBC patients has little effect on the ICER

	Lloyd	Peasgood		
		1	2	3
PFS Bev+Cap	0.7842	0.7435	0.9132	0.8817
PFS Cap	0.7736	0.7569	0.8984	0.8679
PROGRESSION	0.4961	0.4880	0.4350	0.4350
ICER	**£77,318**	**£79,991**	**£77,851**	**£79,147**

The results suggest that this alternative source of utility estimates has very little influence on the ICER.

Comparison against vinorelbine

Vinorelbine has previously been assumed to have equivalent efficacy when compared to capecitabine (NICE CG81 2009). When the comparator arm of the model is assumed to incur the drug acquisition and administration costs consistent with an intravenous branded vinorelbine regimen, the base case ICER is almost the same as the base case comparison against capecitabine at £76,199. As expected, bevacizumab + capecitabine is less cost effective against generic vinorelbine (assuming acquisition costs are consistent with those reported by the Commercial Medicines Unit (Commercial Medicines Unit 2011). In contrast, bevacizumab + capecitabine combination therapy is more cost effective against an oral formulation of vinorelbine, with an ICER of £58,972.

Table 42: incremental cost-effectiveness of bevacizumab + capecitabine against vinorelbine formulations

	Capecitabine base case	Vinorelbine generic (IV)	Navelbine (IV)	Navelbine (oral)
Average drug cost per month	£312.41	£77.29	£449.99	£1995.70
Cost of administering drug (month 1)	£255.32	£338.94	£338.94	£255.32
Cost of administering drug (subsequent months)	£255.32	£196.09	£196.09	£255.32
ICER	£77,318	£80,260	£76,198	£58,972

6.6.10 What were the main findings of each of the sensitivity analyses?

The univariate sensitivity analysis demonstrates that the model is most sensitive to utilities and costs for patients with progressed disease (Table 40), while the PSA suggests that there is less than a 0.1% chance that the ICER for the addition of bevacizumab to capecitabine is less than £50,000 per QALY.

6.6.11 What are the key drivers of the cost-effectiveness results?

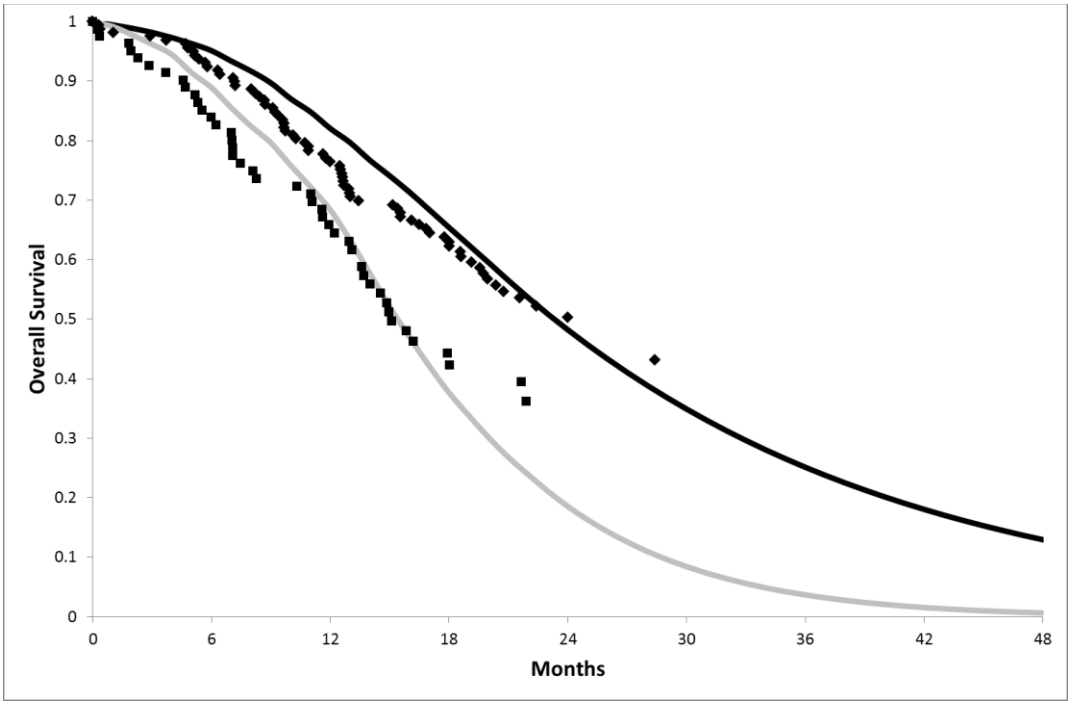
The key drivers of the cost-effectiveness results are the cost of bevacizumab, the cost and utility of progressed disease and the parametric function describing PFS and PD.

6.7 Validation

6.7.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Since the model does not directly use the overall survival of patients observed in the RIBBON-1 trial, these data were used as a reference point to ensure that the mortality predicted in the model was a fair reflection of what was observed (Figure 23).

Figure 23: Comparison of modelled (lines) and observed (markers) overall survival of patients



This indicates that the model tends to overestimate survival in both arms of the trial for the first 12 (capecitabine arm) and 18 (bevacizumab and capecitabine arm) months.

6.8 Subgroup analysis

No further analysis of subgroups (beyond the base case analysis provided) was undertaken in this submission.

6.9 Interpretation of economic evidence

6.9.1 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?

There are no economic evaluations in this indication and patient population with which these results may be compared.

6.9.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

This economic evaluation is only relevant to patients with similar characteristics to those randomised to the capecitabine arms of RIBBON-1, who had previously been treated with a taxane. Given recent clinical guidelines (NICE CG81 2009), concerning the recommended treatment pathway for patients with mBC, it is assumed that patients previously treated with a taxane will have already received or been considered for treatment with an anthracycline. Therefore, the patient cohort in this model is a close approximation for the target population identified in the decision problem.

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

Strengths of this evaluation include; the use of observations from the pivotal clinical trial (RIBBON-1) wherever possible, resource use and costs based on recent UK clinical guidelines and reference costs, robust utilities for disease states based on accepted sources and close adherence to the target population described in the decision problem.

The main weakness of the evaluation is that it is based on a post-hoc subgroup analysis of prior-adjuvant taxane treated patients. Whilst this subgroup effect has been identified in three separate large RCTs of bevacizumab, further research is required to fully confirm the strong clinical (PFS & OS) benefits of bevacizumab for prior-adjuvant taxane treated metastatic breast cancer patients.

6.9.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

No further analyses are required to support the robustness of these results. This analysis has demonstrated that bevacizumab is not a cost-effective use of NHS resource with respect to the standard cost-effectiveness threshold of £30,000 per QALY gained.

Section C – Implementation

7 Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

As in Section 2.2, we have calculated the number of patients in Year 1 to be 773 which covers this indication/subgroup exclusively. We have assumed a population growth rate of 0.5% per year and so in Year 2 there are 777 patients, Year 3 781, Year 4 785 and Year 5 789 patients.

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Capecitabine monotherapy is assumed to be the standard of care and therefore most likely treatment option, given the scope of the appraisal and the estimated number of eligible patients (presented in Section 7.1 above) focuses strictly on this population.

7.3 What assumption(s) were made about market share (when relevant)?

Following positive recommendation, it is assumed that in Year 1 uptake of bevacizumab will be 10%, 20% in Year 2, 30% in Year 3, 40% in Year 4 and 50% in Year 5.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

All relevant costs have been considered within the economic model and the budget impact model utilises these costs entirely.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

All unit costs were based on national reference costs or adverse event costs from the trial.

7.6 Were there any estimates of resource savings? If so, what were they?

There were not.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The budget impact model follows 5 separate cohorts of patients over the 5 years, and different years of a patients' treatment have separate and different costs. It is misleading to present an annual budget impact since in the first year (2012) only cohort 1 is being treated. Results are present for the 5 years 2012 – 2016 below:

	After Recommendation Impact	Before Recommendation Impact	Incremental Impact	Total
2012	£8,973,342.35	£6,626,644.32	£2,346,698.03	
2013	£17,909,782.29	£13,122,319.83	£4,787,462.46	
2014	£20,826,698.80	£13,187,931.43	£7,638,767.37	
2015	£23,772,336.73	£13,253,871.09	£10,518,465.64	
2016	£26,746,910.36	£13,320,140.44	£13,426,769.92	**£38,718,163.41**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No.

8 References

References

Anderson, W. F., Jatoi, I., & Devesa, S. S. 2005, "Distinct breast cancer incidence and prognostic patterns in the NCI's SEER program: suggesting a possible link between etiology and outcome", *Breast Cancer Res Treat.*, vol. 90, no. 2, pp. 127-137.

Burstein, H., Harris, J., & Morrow, M. 2008, "Malignant tumors of the breast," in *Cancer: Principles and Practice of Oncology.*, 8th edn, V. DeVita, T. Lawrence, & S. Rosenberg, eds., Lippincott Williams & Wilkins, Philadelphia,PA,USA, pp. 1606-1654.

Cancer Research UK. CancerStats: Breast Cancer Incidence – UK. May 2009. http://publications.cancerresearchuk.org/WebRoot/crukstoredb/CRUK_PDFs/CSBREA09.pdf. 2009. 23-10-2011.
Ref Type: Electronic Citation

Cancer Research UK. Table 1.1: Breast Cancer (C50), Number of New Cases, Crude and European Age-Standardised (AS) Incidence Rates per 100,000 Population, UK, 2008. http://info.cancerresearchuk.org/cancerstats/types/breast/incidence/ . 18-7-2011. 26-10-2011.
Ref Type: Electronic Citation

Commercial Medicines Unit. Electronic Market Information Tool. http://cmu.dh.gov.uk/electronic-market-information-tool-emit/ . 2011. Department of Health.
Ref Type: Electronic Citation

Data on File 2011, "RXUKDONF00003", *Roche Data on File*.

Dent, R., Trudeau, M., Pritchard, K. I., Hanna, W. M., Kahn, H. K., Sawka, C. A., Lickley, L. A., Rawlinson, E., Sun, P., & Narod, S. A. 2007, "Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence", *Clinical Cancer Research*, vol. 13, no. 15, pp. 4429-4434.

Department of Health 2011, *NHS reference costs 2009-2010*, Department of Health.

Dolan, P., Gudex, C., Kind, P., & Williams, A. 1996, "The time trade-off method: Results from a general population study", *Health Economics*, vol. 5, no. 2, pp. 141-154.

Dranitsaris, G., Leung, P., Mather, J., & Oza, A. 2000, "Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: A comparison of two aromatase inhibitors to megestrol acetate", *Anti-Cancer Drugs*, vol. 11, no. 7, pp. 591-601.

Fleeman, N., Bagust, A., Boland, A., Dickson, R., Dundar, Y., Moonan, M., Oyee, J., Blundell, M., Davis, H., Armstrong, A., & Thorp, N. 2010, *Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2*, NIHR HTA Programme (Project No. 09/101/01.

Glaspy, J., Dieras, V., Brufsky, A., Miles, D. W., Phan, S. C., & Shaughnessy, J. 2010, "Bevacizumab (BV) in combination with chemotherapy in the treatment of HER2-negative metastatic breast cancer (mBC): PFS subgroup results from two phase III studies", *EJC Supplements*, vol. 8, no. 3, p. 202.

Gray, R., Bhattacharya, S., Bowden, C., Miller, K., & Comis, R. L. 2009, "Independent review of E2100: a phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer", *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, vol. 27, pp. 4966-4972.

Helgeson, V. S. & Tomich, P. L. 2005, "Surviving cancer: a comparison of 5-year disease-free breast cancer survivors with healthy women", *Psychooncology.*, vol. 14, no. 4, pp. 307-317.

Herschbach, P., Keller, M., Knight, L., Brandl, T., Huber, B., Henrich, G., & Marten-Mittag, B. 2004, "Psychological problems of cancer patients: a cancer distress screening with a cancer-specific questionnaire", *Br J Cancer.*, vol. 91, no. 3, pp. 504-511.

IARC. World cancer report 2003. http://www.iarc.fr/en/publications/pdfs-online/wcr/2003/index.php . 2003. 21-9-2011.
Ref Type: Electronic Citation

Joint Formulary Committee. British National Formulary. 62. 2011. London, BMJ Goup and Pharmaceutical Press.
Ref Type: Serial (Book,Monograph)

Jones, S. E. 2008, "Metastatic breast cancer: the treatment challenge", *Clin Breast Cancer.*, vol. 8, no. 3, pp. 224-233.

Leung, P., Tannock, I. F., Oza, A. M., Puodziunas, A., & Dranitsaris, G. 1999, "Cost-utility analysis of chemotherapy using paclitaxel, docetaxel, or vinorelbine for patients with anthracycline-resistant breast cancer", *Journal of Clinical Oncology*, vol. 17, no. 10, pp. 3082-3090.

Lloyd, A., Nafees, B., Narewska, J., Dewilde, S., & Watkins, J. 2006, "Health state utilities for metastatic breast cancer", *British Journal of Cancer*, vol. 95, no. 6, pp. 683-690.

Miles, D. W. 2010, "Meta-analysis of patients previously treated with taxanes from three randomised trials of bevacizumab and first-line chemotherapy as treatment for metastatic breast cancer", *European Journal of Cancer*, vol. #279PD, no. ESMO Conference.

Miles, D., Chan, A., Dirix, L., Cortθs, J., Pivot, X., Tomczak, P., Delozier, T., Sohn, J., Provencher, L., Puglisi, F., Harbeck, N., Steger, G., Schneeweiss, A., Wardley, A., Chlistalla, A., & Romieu, G. 2010, "Phase III study of bevacizumab plus docetaxel compared with placebo plus docetaxel for the first-line treatment of human epidermal

growth factor receptor 2-negative metastatic breast cancer", *Journal of Clinical Oncology*, vol. 28, no. 20, pp. 3239-3247.

Millar, D. R., Corrie, P., Hill, M., & Pulfer, A. PCN74 A SERVICE EVALUATION TO COMPARE SECONDARY CARE RESOURCE USE BETWEEN XELOX AND FOLFOX-6 REGIMENS IN THE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC) FROM A UK NATIONAL HEALTH SERVICE (NHS) PERSPECTIVE. Value in Health 11[6], A483. 1-11-2008.
Ref Type: Abstract

Muss, H. B., Smith, L. R., & Cooper, M. R. 1987, "Tamoxifen rechallenge: response to tamoxifen following relapse after adjuvant chemohormonal therapy for breast cancer", *J Clin Oncol.*, vol. 5, no. 10, pp. 1556-1558.

NICE. Guide to Methods of Technology Appraisal. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf . 23-6-2008. National Institute for Health and Clinical Excellence. 25-10-2011.
Ref Type: Electronic Citation

NICE 2009, *Breast cancer (early & locally advanced): diagnosis and treatment Clinical Guideline 80 (CG80).*, National Institute for Health and Clinical Excellence (NICE).

NICE CG81 2009, "National Institute for Health and Clinical Excellence (NICE); Winstanley J & Murray N. (2009) Advanced breast cancer: diagnosis and treatment, Clinical Guideline 81 (CG81). February 2009.", *Accessed online 21/09/10 at: http://guidance.nice.org.uk/CG81.*

O'Shaughnessy, J. 2005, "Extending survival with chemotherapy in metastatic breast cancer", *Oncology 10 Suppl 3:20-9.* pp. 20-29.

Office of National Statistics 2011a, *Mid-2010 Population Estimates: England; estimated resident population by single year of age and sex.*, Office of National Statistics.

Office of National Statistics 2011b, *Mid-2010 Population Estimates: Wales; estimated resident population by single year of age and sex.*, Office of National Statistics.

Pajk, B., Cufer, T., Canney, P., Ellis, P., Cameron, D., Blot, E., Vermorken, J., Coleman, R., Marreaud, S., Bogaerts, J., Basaran, G., & Piccart, M. 2008, "Anti-tumor activity of capecitabine and vinorelbine in patients with anthracycline- and taxane-pretreated metastatic breast cancer: Findings from the EORTC 10001 randomized phase II trial", *The Breast*, vol. 17, no. 2, pp. 180-185.

Peasgood, T., Ward, S., & Brazier, J. 2010, "Health-state utility values in breast cancer", *Expert Review of Pharmacoeconomics and Outcomes Research*, vol. 10, no. 5, pp. 553-566.

PSSRU 2010, *Unit Costs of Health and Social Care 2010*, Personal Social Services Research Unit, Canterbury, Kent.

Ravdin, P. M., Green, S., Dorr, T. M., McGuire, W. L., Fabian, C., Pugh, R. P., Carter, R. D., Rivkin, S. E., Borst, J. R., Belt, R. J., & . 1992, "Prognostic significance of progesterone receptor levels in estrogen receptor-positive patients with metastatic

breast cancer treated with tamoxifen: results of a prospective Southwest Oncology Group study", *J Clin Oncol.*, vol. 10, no. 8, pp. 1284-1291.

Roche Data on File. RXUKDONF00118: Xeloda Breast Cancer Opportunity Research Wave 6. 2011.
Ref Type: Data File

Rodgers, M., Soares, M., Epstein, D., Yang, H., Fox, D., & Eastwood, A. 2010, *Bevacizumab in combination with a taxane for the first-line treatment of HER2-negative metastatic breast cancer.*, NIHR HTA Programme (Project No. HTA 09/25).

Scarborough, P., Bhatnagar, P., Wickramasinghe, K., Smolina, K., Mitchell, C., & Rayner, M. 2010, *Coronary heart disease statistics: 2010 edition*, Department of Public Health, University of Oxford, Oxford, UK.

Shaughnessy, J., Dieras, V., Glaspy, J., Brufsky, A., Miller, K. D., Miles, D. W., Koralewski, P., Phan, S. C., & Bhattacharya, S. 2009, "Comparison of Subgroup Analyses of PFS from Three Phase III Studies of Bevacizumab in Combination with Chemotherapy in Patients with HER2- Negative Metastatic Breast Cancer (MBC)", *Cancer Research*, vol. 69, no. 24, p. 512S.

The American Economic Association & EconLIT. EconLIT search database. http://www.aeaweb.org/econlit/efm/index.php . 2011. 2-12-0011.
Ref Type: Electronic Citation

University of York. Centre for Reviews and Dissemination. http://www.crd.york.ac.uk/crdweb/HomePage.asp . 2011.
Ref Type: Electronic Citation

Wood, W., Muss, H., Solin, L., & Olopade, O. 2005, "Malignant tumors of the breast.," in *Cancer: Principles and Practice of Oncology*, 7th edn, V. DeVita, T. Lawrence, & S. Rosenberg, eds., Lippincott Williams & Wilkins., Philadelphia, PA, USA.

Xeloda SPC. Xeloda Summary of Product Characteristics. http://www.medicines.org.uk/EMC/medicine/4619/SPC/Xeloda+150mg+and+500mg+Film-coated+Tablets/ . 30-6-2011. 26-10-2011.
Ref Type: Electronic Citation

Zielinski, C., Zielinski, C., Gralow, J., Gralow, J., Martin, M., & Martin, M. 2010, "Optimising the dose of capecitabine in metastatic breast cancer: confused, clarified or confirmed?", *Annals of Oncology*, vol. 21, no. 11, pp. 2145-2152.

9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 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.

The following databases were searched:

Dialog DataStar, Medline (MEYY)

Dialog DataStar, Medline-In process (MEIP)

Dialog DataStar, Embase (EMYY)

Dialog DataStar, Embase latest eight weeks (EMBA)

Dialog DataStar, Biosis Previews (BIYY)

Dialog DataStar, Biosis Previews - latest eight weeks (BIOX)

The Cochrane Library

American Society of Clinical Oncology (ASCO) abstracts

San Antonio Breast Cancer Symposium (SABCS) abstracts

European CanCer Organisation (ECCO) and European Society for Medical Oncology (ESMO) abstracts:

ECCO/ESMO 2011

ESMO 2010

ECCO/ESMO 2009

ESMO 2008

ECCO 2007

ESMO 2007

9.2.2 **The date on which the search was conducted.**

MEYY, EMYY, EMBA, MEIP, BIYY were searched on 15th November 2011

ASCO, SABCS, ESMO and ECCO abstracts and the Cochrane library were searched on the 14th November 2011.

9.2.3 **The date span of the search.**

Dialog DataStar, Embase 1993 to 15th November 2011 (EMYY)

Dialog DataStar, Embase latest eight weeks prior to 15th November 2011 (EMBA)

Dialog DataStar, Medline 1993 to 15th November 2011 (MEYY)

Dialog DataStar, Medline-In process-Latest eight weeks prior to 15th November 2011 (MEIP)

Dialog DataStar, Biosis Previews 1993 to 15th November 2011 (BIYY)

Dialog DataStar, Biosis Previews Last update. Latest 8 weeks prior to 15th November 2011 (BIOX).

The Cochrane Library, http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html - searched with unrestricted dates to 14th November 2011.

ASCO abstracts, Journal of Clinical Oncology archives online http://jco.ascopubs.org/search.dtl, entries from 2004 to 14th November 2011.

San Antonio Breast Cancer Symposium (SABCS) abstracts, Cancer Research Journal archives online, http://cancerres.aacrjournals.org/search entries from 2006 to 154h November 2011.

ECCO/ESMO abstracts, 2007-2011:

ECCO/ESMO 2011 –

http://new.ecco.org.eu/ecco_content/2011StockholmAbstractbook/index.html#/101/zoomed

ESMO 2010 - Annals of Oncology 2010; 21 (suppl 8): http://annonc.oxfordjournals.org/content/21/suppl_8

ECCO/ESMO 2009 – Conference poster CD

ECCO 2007 - http://www.posters2view.com/ecco14/welcome.php

ESMO 2008 - Annals of Oncology 2008; 19 (Suppl 8): viii2-viii321

ESMO 2007 - Annals of Oncology 2007; 18 (Suppl 9): ix1-ix207

9.2.4 **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).**

Search strategy for EMBASE 1993 – 15th November 2011

No	Database	Search term	Info added since	Results
1	EMYY	CLINICAL-TRIAL#	unrestricted	764266
2	EMYY	Randomized	unrestricted	395959
3	EMYY	1 AND 2	unrestricted	296889
4	EMYY	3 AND LG=EN AND HUMAN=YES	unrestricted	267190
5	EMYY	breast ADJ cancer	unrestricted	176347
6	EMYY	BREAST-CANCER#.DE.	unrestricted	163449
7	EMYY	metastatic ADJ breast ADJ cancer	unrestricted	7082
8	EMYY	advanced ADJ breast ADJ cancer	unrestricted	4409
9	EMYY	5 OR 6 OR 7 OR 8	unrestricted	198152
10	EMYY	Bevacizumab	unrestricted	17339
11	EMYY	BEVACIZUMAB#.W..DE.	unrestricted	16985
12	EMYY	216974-75-3	unrestricted	16991
13	EMYY	10 OR 11 OR 12	unrestricted	17339
14	EMYY	Capecitabine	unrestricted	10275
15	EMYY	CAPECITABINE#.W..DE.	unrestricted	10048
16	EMYY	154361-50-9	unrestricted	10048
17	EMYY	14 OR 15 OR 16	unrestricted	10275
18	EMYY	13 AND 17	unrestricted	3273
19	EMYY	9 AND 18	unrestricted	1145
20	EMYY	4 AND 19	unrestricted	117
21	EMYY	REVIEW=YES	unrestricted	1396184
22	EMYY	20 NOT 21	unrestricted	48

9.2.5

Search strategy for MEDLINE: 1993 – 15th November 2011

9.2.6

No	Database	Search term	Info added since	Results
1	MEYY	CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#	unrestricted	507390
2	MEYY	Randomized	unrestricted	403554
3	MEYY	1 AND 2	unrestricted	256091
4	MEYY	3 AND LG=EN AND HUMAN=YES	unrestricted	235289
5	MEYY	Bevacizumab	unrestricted	5767
6	MEYY	Capecitabine	unrestricted	2911
7	MEYY	5 AND 6	unrestricted	317
8	MEYY	breast ADJ cancer	unrestricted	122505
9	MEYY	BREAST-NEOPLASMS#.DE.	unrestricted	130514
10	MEYY	metastatic ADJ breast ADJ cancer	unrestricted	6232
11	MEYY	advanced ADJ breast ADJ cancer	unrestricted	3917
12	MEYY	8 OR 9 OR 10 OR 11	unrestricted	163408
13	MEYY	7 AND 12	unrestricted	57
14	MEYY	4 AND 13	unrestricted	2

9.2.7

Search strategy for BIOSIS: 1993 – 15th November 2011

No	Database	Search term	Info added since	Results
1	BIYY	metastatic ADJ breast ADJ cancer	unrestricted	6098
2	BIYY	BREAST-NEOPLASMS.DS. OR METASTATIC-BREAST-CANCER.DS. OR BREAST-CANCER.DS.	unrestricted	101494
3	BIYY	1 OR 2	unrestricted	102849
4	BIYY	Bevacizumab	unrestricted	3881
5	BIYY	Capecitabine	unrestricted	2490
6	BIYY	4 AND 5	unrestricted	274
7	BIYY	3 AND 6	unrestricted	83
8	BIYY	7 AND HUMANS#	unrestricted	82
9	BIYY	PT=LITERATURE-REVIEW	unrestricted	515164
10	BIYY	8 NOT 9	unrestricted	62

9.2.8

Search strategy for EMBASE: 1993 – 15th November 2011 (last 8 weeks)

No	Database	Search term	Info added since	Results
1	EMBA	Bevacizumab	unrestricted	203
2	EMBA	Capecitabine	unrestricted	59
3	EMBA	breast ADJ cancer	unrestricted	1697
4	EMBA	1 AND 2 AND 3	unrestricted	4

9.2.9

Search strategy for MEDLINE: 1993 – 15th November 2011 (last 8 weeks)

No	Database	Search term	Info added since	Results
1	MEIP	Bevacizumab	unrestricted	514
2	MEIP	Capecitabine	unrestricted	137
3	MEIP	breast ADJ cancer	unrestricted	4845
4	MEIP	1 AND 2 AND 3	unrestricted	7

9.2.10

Search strategy for BIOSIS: 1993 – 15th November 2011 (last 8 weeks)

No.	Database	Search term	Info added since	Results
1	BIOX	Bevacizumab	unrestricted	12
2	BIOX	Capecitabine	unrestricted	2
3	BIOX	breast ADJ cancer	unrestricted	155
4	BIOX	1 AND 2 AND 3	unrestricted	0

9.2.11

Search strategy for Cochrane library – 14th November 2011

The Cochrane Library was searched with unrestricted dates. The search was conducted using the terms "*bevacizumab"* in Title, Abstract or Keywords AND "*metastatic breast cancer"* in Title, Abstract or Keywords. The search was re-run using the terms "*bevacizumab"* in Title, Abstract or Keywords AND "*advanced breast cancer"* in Title, Abstract or Keywords, and records manually combined from both searches.

Search strategy for ASCO abstracts: January 2004 – 14th November 2011

The *Journal of Clinical Oncology* archive was searched for ASCO annual meetings 2004-2011. ASCO Meeting Abstracts was specified as the source to search. The search was conducted through the *Journal of Clinical Oncology* archive rather than the ASCO website as the search tool on the website has restricted function compared with the *Journal of Clinical Oncology* archive, which allows compound searching in multiple fields. The search was conducted using the terms "*bevacizumab"* in the Title and "*metastatic breast cancer"* in the Title or Abstract and "*capecitabine"* in the Title or Abstract or Keyword. A second search was conducted using the terms "*bevacizumab"* in the Title and *"advanced breast cancer"* NOT "*metastatic breast cancer"* in the Title or Abstract and "*capecitabine"* in the Title or Abstract or Keyword. The results of these two searches were combined and duplicates dropped manually.

Search strategy for SABCS abstracts: January 2007 – 14th November

2011

San Antonio Breast Cancer Symposium (SABCS) abstracts were searched online in the *Cancer Research Journal*: http://cancerres.aacrjournals.org/search . Meeting Abstracts were selected as the source of the search. Abstracts are available online from 2007 to the present. Search includes entries up until 14th November 2011. The search was conducted using the terms "*bevacizumab"* in the Title, "*metastatic breast cancer"* in the Title or Abstract and "*capecitabine"* in the Title or Abstract or Keyword. A second search was conducted using the terms "*bevacizumab"* in the Title, *"advanced breast cancer"* NOT "*metastatic breast cancer"* in the Title or Abstract and and "*capecitabine"* in the Title or Abstract or Keyword. The results of these two searches were combined and duplicates dropped manually.

Search strategy for ECCO/ESMO abstracts: 2007 to the 14th November 2011

The ECCO conference takes place every 2 years in combination with an ESMO conference, and the ESMO conference arises annually. Abstracts for joint ECCO-ESMO conferences are published in abstract books or are available on line, whereas when an ESMO conference arises alone, abstracts are published in the *Annals of Oncology*.

ECCO-ESMO Abstracts

In 2011, a joint ECCO-ESMO conference took place, with abstracts (including late breaking abstracts) published online on the conference website: http://stockholm2011.ecco-org.eu/Programme.aspx and the abstracts from the ECCO-ESMO conference in 2009 were made available from the conference CD. Abstracts from the ECCO 2007 conference were searched online at: http://www.posters2view.com/ecco14/welcome.php . The searches were conducted using the free text term '*bevacizumab'*. Once an abstract included this term, the abstract was read for inclusion of information on breast cancer. The search was repeated using '*Avastin*' and '*breast cancer'* as free-text search terms. Abstracts were deemed relevant for analysis if they mentioned *"bevacizumab"* or "*Avastin"* AND "*breast cancer"* AND "capecitabine" or "Xeloda".

ESMO abstracts

The Annals of Oncology publish abstracts from ESMO. Within each website, separate PDF abstract books are available. The abstracts from these meetings in 2007, 2008 and 2010 were accessed via the following websites:

ESMO 2010: http://annonc.oxfordjournals.org/content/21/suppl_8.

ESMO 2008: http://annonc.oxfordjournals.org/content/19/suppl_8.toc

ESMO 2007: http://annonc.oxfordjournals.org/content/18/suppl_9.toc

The following abstract books were searched using the free text term "*bevacizumab*" and "*Avastin*", if an article included the drug name it was read for mention of breast cancer. Abstracts were deemed relevant for analysis if they mentioned *bevacizumab* or *Avastin* and *breast cancer*.

The following individual abstract books were assessed:

Abstract books from ESMO 2010:

Hamilton fairley award, *Ann Oncol* (2010) 21(suppl 8): viii21.

Special Symposium: Overcoming disparities in cancer control in Europe, Ann Oncol (2010) 21(suppl 8): viii33.

Special Symposium: Toxicities of targeted therapies: Prevention and management, Ann Oncol (2010) 21(suppl 8): viii34.

ESMO/ASCO Joint Symposium: The future of antiangiogenesis therapy, Ann Oncol (2010) 21(suppl 8): viii37,

ESMO 2010 late-breaking abstracts, Ann Oncol (2010) 21(suppl 8): NP, Breast cancer, advanced Ann Oncol (2010) 21(suppl 8): viii96-viii121

Abstract books from ESMO 2008:

Hamilton fairley award, Ann Oncol (2008) 19(suppl 8): viii21

ESMO special symposium: large scale molecular analyses for target discovery: from the bedside to the bench, Ann Oncol (2008) 19(suppl 8): viii26-viii27,

ESMO special symposium: emerging new targeted drugs, Ann Oncol (2008) 19(suppl 8): viii34,

ESMO/ASCO joint symposium: assessing, reporting and managing the safety of oncology drugs, Ann Oncol (2008) 19(suppl 8): viii39-viii40,

oncology highlights 2008, Ann Oncol (2008) 19(suppl 8): viii44-viii46,

ESMO 2008 late-breaking abstracts, Ann Oncol (2008) 19(suppl 8): NP,

ESMO special symposium: innovation in breast cancer care: selecting the best patient, exploring new treatment targets Ann Oncol (2008) 19(suppl 8): viii28-viii29,

Breast cancer, advanced Ann Oncol (2008) 19(suppl 8): viii63-viii76 doi:10.1093/annonc/mdn504.

Abstract books from ESMO 2007: breast cancer

Ann Oncol (2007) 18(suppl 9): ix161-ix162,

European school of oncology symposium: new drug development Ann Oncol (2007) 18(suppl 9): ix157-ix158 article:

molecular mechanism implemented in clinical practice, Ann Oncol (2007) 18(suppl 9): ix187 doi:10.1093/annonc/mdm324,

symposium article: breast cancer, advanced Ann Oncol (2007) 18(suppl 9): ix163-ix164 doi:10.1093/annonc/mdm315

9.2.12 Details of any additional searches, such as searches of company databases (include a description of each database).

None.

9.2.13 The inclusion and exclusion criteria.

Inclusion criteria

Published papers or abstracts which evaluated the following were included:

Bevacizumab had to be the major focus of the study, in order to eliminate references which merely mentioned bevacizumab as part of a discussion of treatments for metastatic breast cancer or other cancers

Metastatic breast cancer had to be a major focus of the study, in order to eliminate papers addressing the use of bevacizumab in other types of breast cancers, e.g., inflammatory breast cancer, or in other settings, e.g., neoadjuvant/adjuvant breast cancer, early breast cancer

Studies in which patients received bevacizumab therapy in combination with capecitabine, to be consistent with the bevacizumab licence. Data addressing the efficacy of bevacizumab in combination with other agents are not in line with this submission.

Studies in which patients received study therapy for the first-line treatment of metastatic breast cancer, to be consistent with the bevacizumab licence. Data

addressing the efficacy of bevacizumab in combination with capecitabine in second or later lines of treatment are not in line with the licence.

Patient population had to consist predominantly of HER2-negative patients (≥90%), as this is the patient population of interest for this appraisal

Efficacy endpoints associated with the treatment of metastatic breast cancer were the focus for the data, i.e., progression-free survival, overall survival, response rates

Clinical trial data – rather than case reports, retrospective reviews, etc.

Controlled studies

Documents relating to humans – since work in animal models is not relevant to this application

Exclusion criteria

Searches took place and references imported to Reference Manager 11, where de-duplication arose. Before publications were assessed using exclusion criteria below, papers were removed if: a) bevacizumab was not used as the experimental drug, b) research was not performed in humans, and if c) research was not in breast cancer. These papers should not have been included in the output of searches; however, due to the limited precision of reference search programs, some irrelevant journals were selected.

Published papers or abstracts which evaluated the following were excluded:

- References which were not randomised, controlled phase II/III trials (such as phase I or safety studies or reviews).
- Studies where capecitabine was not included, or where the difference between treatment arms was the addition of an agent other than bevacizumab (e.g., capecitabine + bevacizumab vs capecitabine + bevacizumab + agent A).
- Studies which were in non-relevant populations, i.e. non first-line setting in metastatic disease, neoadjuvant/adjuvant therapy, early breast cancer, locally advanced breast cancer only or inflammatory breast cancer, HER2-positive disease.

- Studies where the dose or regimen of bevacizumab or capecitabine used was not UK standard practice.

- References from ongoing studies providing insufficient data e.g. patients demographics/study designed described, but no efficacy data available.

9.2.14 **The data abstraction strategy.**

Abstracts were obtained for each of the RCT records identified and assessed for relevance. Where it was not possible to determine relevance from the abstract the full paper or record was obtained and evaluated in more detail. For each excluded RCT, a rationale was recorded.

Exclusion Key:

References which were not randomised, controlled phase II/III trials (such as phase I, reviews and meta-analyses).	**RAN**
Studies where capecitabine was not included in combination with bevacizumab, or where capecitabine is in combination with other anti-cancer agents or where capecitabine + bevacizumab is not compared to capecitabine alone	**CHE**
Studies which were in non-relevant populations, i.e. non first-line setting in metastatic disease, neoadjuvant/adjuvant therapy, early breast cancer, locally advanced breast cancer only or inflammatory breast cancer, HER2-positive disease, except for the purposes of providing key safety data.	**POP**

Search results from EMBASE 1993 – 15th November 2011

9 articles were removed due to not studying bevacizumab, not investigating breast cancer, or examining *in vitro/ ex-vivo* data.

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
EMBASE	1	Not specified	2002	No	RAN
EMBASE	2	Miller K	2003	No	CHE
EMBASE	3	Sledge G	2005	No	RAN
EMBASE	4	Miller K	2005	No	POP
EMBASE	5	Muss H	2006	No	RAN
EMBASE	6	Poole C	2006	No	RAN
EMBASE	7	Moore M	2006	No	RAN
EMBASE	8	Estevez L	2007	No	RAN
EMBASE	9	Scappaticci F	2007	No	RAN
EMBASE	10	Schiavon G	2007	No	RAN
EMBASE	11	Bertino J	2007	No	RAN
EMBASE	12	Folkman J	2007	No	RAN
EMBASE	13	HoQuoc T	2007	No	RAN
EMBASE	14	Heinemann V	2008	No	RAN
EMBASE	15	Mauri D	2008	No	RAN
EMBASE	16	Dawood S	2008	No	RAN
EMBASE	17	Puglisi F	2008	No	RAN
EMBASE	18	Van L	2008	No	RAN
EMBASE	19	Sherrill B	2008	No	RAN
EMBASE	20	Wachter K	2009	No	RAN
EMBASE	21	Labidi	2009	No	CHE
EMBASE	22	Ford R	2009	No	RAN
EMBASE	23	Hapani S	2009	No	RAN
EMBASE	24	Jassem J	2009	No	RAN
EMBASE	25	Geiger G	2010	No	RAN
EMBASE	26	Tsujino K	2010	No	RAN
EMBASE	27	Bartsch R	2010	No	RAN
EMBASE	28	Pagani O	2010	No	RAN
EMBASE	29	AnMao M	2010	No	RAN
EMBASE	30	Guarneri V	2010	No	RAN
EMBASE	31	Tang PA	2010	No	RAN
EMBASE	32	Ranpura V	2010	No	RAN
EMBASE	33	Berrada N	2010	No	RAN
EMBASE	34	Lee J	2011	No	RAN
EMBASE	35	Besse	2010	No	RAN
EMBASE	36	Fridlyand J	2011	No	RAN
EMBASE	37	Hurwitz H	2011	No	RAN
EMBASE	38	Smith IE	2011	No	RAN
EMBASE	39	Robert N	2011	Yes	

Search results from MEDLINE 1993 – 15th November 2011

Both articles from MEDLINE were duplicates of the EMBASE search.

Search results from BIOSIS 1993 – 15th November 2011

7 articles were removed due to not studying bevacizumab, not investigating breast cancer, or examining *in vitro/ ex-vivo* data.

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
BIOSIS	1	Miller KD	2002	No	POP
BIOSIS	2	Perez EA	2006	No	CHE
BIOSIS	3	Hudis C	2006	No	RAN
BIOSIS	4	Miller K	2006	No	RAN
BIOSIS	5	Nicolini A	2006	No	RAN
BIOSIS	6	Sledge GW	2006	No	RAN
BIOSIS	7	Greil R	2007	No	CHE
BIOSIS	8	Ferrari B	2007	No	CHE
BIOSIS	9	Miller K	2007	No	RAN
BIOSIS	10	Miles D	2008	No	RAN
BIOSIS	11	Torrisi R	2008	No	CHE
BIOSIS	12	Boulikas T	2008	No	RAN
BIOSIS	13	Cameron D	2008	No	RAN
BIOSIS	14	Harbeck N	2008	No	RAN
BIOSIS	15	Dieras	2009	Yes	
BIOSIS	16	Lang I	2009	Yes	
BIOSIS	17	Robert N	2009	Yes	
BIOSIS	18	Brufsky A	2009	No	POP
BIOSIS	19	Traina TA	2009	No	RAN
BIOSIS	20	Not specified	2009	No	RAN
BIOSIS	21	Bertolini F	2009	No	RAN
BIOSIS	22	Book R	2009	No	RAN
BIOSIS	23	Calleri A	2009	No	RAN
BIOSIS	24	Campagnoli E	2009	No	RAN
BIOSIS	25	Guarneri V	2009	No	RAN
BIOSIS	26	Mancuso P	2009	No	RAN
BIOSIS	27	Robert N	2009	No	RAN
BIOSIS	28	Shaughnessy J	2009	No	RAN
BIOSIS	29	Jackisch	2009	No	RAN
BIOSIS	30	Bondarenko I	2010	Yes	
BIOSIS	31	Brufsky A	2010	Yes	
BIOSIS	32	Dieras V	2010	Yes	
BIOSIS	33	Lindman H	2010	Yes	
BIOSIS	34	Shaughnessy J	2010	Yes	
BIOSIS	35	Fillette A	2010	No	RAN
BIOSIS	36	Jubb A	2010	No	RAN
BIOSIS	37	Barnadas A	2010	No	RAN
BIOSIS	38	Glaspy J	2010	No	RAN
BIOSIS	39	Robert N	2010	No	RAN
BIOSIS	40	Not specified	2010	No	RAN
BIOSIS	41	Dellapasqua S	2011	No	CHE
BIOSIS	42	Inbar M	2011	Yes	

BIOSIS	43	Jubb A	2011	No	POP
BIOSIS	44	Not specified	2011	No	RAN
BIOSIS	45	Bocci G	2011	No	RAN
BIOSIS	46	Ferreira A	2011	No	RAN
BIOSIS	47	Shanbhag S	2011	No	RAN

Search results from EMBASE last 8 weeks prior to – 15th November 2011

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
MEIP	1	Barton S	2011	No	RAN
MEIP	2	Croom K	2011	No	RAN
MEIP	3	Fosker C	2011	No	RAN
MEIP	4	Rastogi P	2011	No	CHE

Search results from MEDLINE last 8 weeks prior to – 15th November 2011

1 article was removed due to not investigating bevacizumab.

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
MEIP	1	Brufsky A	2011	No	POP
MEIP	2	Chirgwin J	2011	No	RAN
MEIP	3	Gajria D	2011	No	RAN
MEIP	4	Spano J	2011	No	RAN

Search results from ASCO – 14th November 2011

6 articles were removed due to not studying bevacizumab, not investigating breast cancer, or examining *in vitro/ ex-vivo* data.

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
ASCO	1	Ordonez J	2006	No	CHE
ASCO	2	Rocca A	2007	No	CHE
ASCO	3	Sledge G	2007	No	RAN
ASCO	4	Greil R	2008	No	CHE
ASCO	5	Locatelli M	2008	No	CHE
ASCO	6	Richardson S	2008	No	RAN
ASCO	7	Rugo HS	2008	No	CHE
ASCO	8	Traina TA	2008	No	PRC
ASCO	9	Locatelli MA	2009	No	CHE
ASCO	10	Pierga J	2009	No	RAN
ASCO	11	Rastogi P	2009	No	CHE
ASCO	12	Robert NJ	2009	Yes	
ASCO	13	Borson R	2010	No	CHE
ASCO	14	Brufsky A	2010	No	POP
ASCO	15	Lang I	2010	Yes	
ASCO	16	O'Shaughnessy J	2010	No	RAN
ASCO	17	Bear HD	2011	No	CHE
ASCO	18	Brufsky A	2011	No	POP
ASCO	19	Brufsky A	2011	No	POP
ASCO	20	Hegewisch-Becker S	2011	No	CHE
ASCO	21	Montero AJ	2011	No	RAN
ASCO	22	Veiga R	2011	No	RAN

Search results from ECCO/ESMO – 14th November 2011

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
ESMO	1	Schneeweiss	2008	No	CHE
ESMO	2	Dellapasqua	2008	No	CHE
ECCO ESMO	3	Cortes-Funes	2009	No	CHE
ESMO	4	Rochlitz	2009	No	RAN
ESMO	5	Foerster	2009	No	RAN
ESMO	6	Miles	2010	No	RAN
ESMO	7	Miles	2010	No	RAN
ESMO	8	Phan	2010	No	CHE
ESMO	9	Lang	2010	Yes	
ESMO	10	Zaiss	2010	No	RAN

Search results from SABCS 2002 – 14th November 2011

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
SABCS	1	Dickler M	2009	No	CHE
SABCS	2	Thomssen C	2010	No	RAN
SABCS	3	Musolino A	2011	No	CHE
SABCS	4	Nasim S	2011	No	RAN
SABCS	5	O'Shaughnessy J	2011	No	RAN
SABCS	6	Salvador J	2011	No	CHE

Search results from Cochrane – 14th November 2011

12 articles were removed due to not studying bevacizumab, not investigating breast cancer, or examining *in vitro/ ex-vivo* data.

Search Database	Result number	Publication author	Publication year	Relevant RCT	Reason for exclusion
COCHRANE	1	Langmuir G	2001	No	POP
COCHRANE	2	Comis RL	2002	No	CHE
COCHRANE	3	Burstein HJ	2004	No	CHE
COCHRANE	4	Kabbinavar FF	2004	No	RAN
COCHRANE	5	Miller K	2005	No	CHE
COCHRANE	6	Klencke BJ	2006	No	RAN
COCHRANE	7	Hambleton J	2006	No	POP
COCHRANE	8	Guardino E	2007	No	CHE
COCHRANE	9	Miller K	2007	No	CHE
COCHRANE	10	Brufsky AM	2008	No	CHE
COCHRANE	11	Klencke BJ	2008	No	CHE
COCHRANE	12	Greil R	2009	No	CHE
COCHRANE	13	Conlin AK	2009	No	CHE
COCHRANE	14	Gray R	2009	No	CHE
COCHRANE	15	Hoelzer KL	2009	No	CHE
COCHRANE	16	Hurvitz SA	2010	No	CHE
COCHRANE	17	Mayer EL	2010	No	CHE
COCHRANE	18	Miles DW	2010	No	CHE
COCHRANE	19	Valachis A	2010	No	RAN
COCHRANE	20	Martin M	2011	No	CHE

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 **A suggested format for the quality assessment of RCT(s) is shown below.**

RIBBON-1		
Study question	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was randomisation carried out appropriately?	After written consent was obtained and eligibility established, the study site obtained the patient's identification number and randomisation to treatment arm from the interactive voice response system	yes
Was the concealment of treatment allocation adequate?	The side effect profile of bevacizumab may have given the investigators some insight into which treatment the patients had been allocated. A placebo control was used to minimise bias	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The patient demographics and characteristics were generally well balanced in both arms of the capecitabine cohort. However there were slightly less triple negative patients and slightly more hormone receptor positive patients in the bevacizumab plus capecitabine arm.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The study was designed as 'double-blind'. A placebo control was used to minimise bias in the assessment of disease response and adverse event reporting	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in drop outs	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no evidence to suggest this	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Efficacy analyses were conducted on the intention to treat population. Safety analyses were conducted on patients who received at least one dose of study medication	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

No indirect comparisons were required as relevant comparators were observed in the RIBBON-1 trial.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

No indirect comparisons were required as relevant comparators were observed in the RIBBON-1 trial.

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence). The following information should be provided.

Non-RCT evidence was not assessed.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

Non-RCT evidence was not assessed.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

Safety was a secondary endpoint and was covered in results from the RIBBON-1 trial.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

N/A

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 **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
- EconLIT
- NHS EED.

Medline

Embase

Medline (R) In-Process

Embase Alert (EMBA)

EconLIT

NHS EED

Medline (MEYY), Embase (EMYY) and Medline in Process (MEIP) were searched using Dialogue Data-Star. NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website. EconLIT was searched via the American Economic Association (AEA) website.

9.10.2 **The date on which the search was conducted.**

Datastar - Wednesday, 16th November 2011

EconLIT and NHS EED – 2nd December 2011

9.10.3 **The date span of the search.**

1993 – 16 November 2011

1993 – 2 December 2011

9.10.4 **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).**

Table 43: Embase search for cost-effectiveness studies

No.	Database	Search term	Info added since	Results
1	EMYY	cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness	unrestricted	379159
2	EMYY	economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost$1 OR direct ADJ cost$1 OR direct ADJ service ADJ cost$1 OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util$3 OR quality ADJ of ADJ life OR QALY OR QALYs OR Qalies	unrestricted	690444
3	EMYY	Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR Evaluation	unrestricted	55773
4	EMYY	(Markov OR decision ADJ analys$2).TI,AB.	unrestricted	11011
5	EMYY	1 AND (2 OR 3 OR 4)	unrestricted	249320
6	EMYY	breast ADJ cancer	unrestricted	176347
7	EMYY	BREAST-CANCER#.DE.	unrestricted	163449
8	EMYY	6 OR 7	unrestricted	198152
9	EMYY	Metastasis#.W..DE. OR metastatic OR advanced OR inoperable	unrestricted	450694
10	EMYY	8 AND 9	unrestricted	49262
11	EMYY	bevacizumab	unrestricted	17339
12	EMYY	BEVACIZUMAB#.W..DE.	unrestricted	16985
13	EMYY	216974-75-3	unrestricted	16991
14	EMYY	11 OR 12 OR 13	unrestricted	17339
15	EMYY	capecitabine	unrestricted	10275
16	EMYY	CAPECITABINE#.W..DE.	unrestricted	10048
17	EMYY	154361-50-9	unrestricted	10048
18	EMYY	15 OR 16 OR 17	unrestricted	10275
19	EMYY	first-line OR 1st-line OR untreated	unrestricted	84637
20	EMYY	5 AND 10 AND 14 AND 18 AND 19	unrestricted	1

Table 44: Embase Alert search for cost-effectiveness studies

No.	Database	Search term	Info added since	Results
1	EMBA	cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness	unrestricted	2529
2	EMBA	economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost$1 OR direct ADJ cost$1 OR direct ADJ service ADJ cost$1 OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util$3 OR quality ADJ of ADJ life OR QALY OR QALYs OR Qalies	unrestricted	1870
3	EMBA	Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR Evaluation	unrestricted	100
4	EMBA	(Markov OR decision ADJ analys$2).TI,AB.	unrestricted	136
5	EMBA	1 AND (2 OR 3 OR 4)	unrestricted	584
6	EMBA	breast ADJ cancer	unrestricted	1697
7	EMBA	Metastasis#.W..DE. OR metastatic OR advanced OR inoperable	unrestricted	3920
8	EMBA	bevacizumab	unrestricted	203
9	EMBA	capecitabine	unrestricted	59
10	EMBA	5 AND 6 AND 7 AND 8 AND 9	unrestricted	0

Table 45: Medline search for cost-effectiveness studies

No.	Database	Search term	Info added since	Results
1	MEYY	cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness	unrestricted	262416
2	MEYY	economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost$1 OR direct ADJ cost$1 OR direct ADJ service ADJ cost$1 OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util$3 OR quality ADJ of ADJ life OR QALY OR QALYs OR Qalies	unrestricted	400893
3	MEYY	Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR Evaluation	unrestricted	51339
4	MEYY	(Markov OR decision ADJ analys$2).TI,AB.	unrestricted	11015
5	MEYY	1 AND (2 OR 3 OR 4)	unrestricted	136653
6	MEYY	breast ADJ cancer	unrestricted	122552
7	MEYY	BREAST-NEOPLASMS#.DE.	unrestricted	130530
8	MEYY	6 OR 7	unrestricted	163457
9	MEYY	metastatic ADJ breast ADJ cancer	unrestricted	6237
10	MEYY	advanced ADJ breast ADJ cancer	unrestricted	3917
11	MEYY	9 OR 10	unrestricted	9346
12	MEYY	bevacizumab	unrestricted	5772
13	MEYY	capecitabine	unrestricted	2911
14	MEYY	5 AND 8 AND 11 AND 12 AND 13	unrestricted	0

Table 46: Medline in Process search for cost-effectiveness studies

No.	Database	Search term	Info added since	Results
1	MEIP	cost OR cost ADJ analysis OR cost ADJ benefit ADJ analysis OR cost ADJ of ADJ illness	unrestricted	8153
2	MEIP	economics OR cost ADJ allocation OR cost ADJ control OR health ADJ care ADJ cost$1 OR direct ADJ cost$1 OR direct ADJ service ADJ cost$1 OR pharmacoeconomics OR cost ADJ utility OR cost ADJ util$3 OR quality ADJ of ADJ life OR QALY OR QALYs OR Qalies	unrestricted	4950
3	MEIP	Models-Economics OR Economics-Medical OR Economics-Pharmaceutical OR Cost-benefit-analysis OR Economic NEAR Evaluation	unrestricted	220
4	MEIP	(Markov OR decision ADJ analys$2).TI,AB.	unrestricted	483
5	MEIP	1 AND (2 OR 3 OR 4)	unrestricted	1611
6	MEIP	breast ADJ cancer	unrestricted	4693
7	MEIP	metastasis#.DE. OR metastatic OR advance OR inoperable	unrestricted	10604
8	MEIP	bevacizumab	unrestricted	508
9	MEIP	capecitabine	unrestricted	133
10	MEIP	5 AND 6 AND 7 AND 8 AND 9	unrestricted	0

NHS EED and EconLIT were search on 02/12/11 with the following strategy:

Costs and cost analysis OR cost benefit analysis OR Economics OR Models-Economics OR Economic Evaluation OR Cost Utility Analysis OR Markov Models

Bevacizumab OR Monoclonal antibodies

Breast Cancer

1 AND 2 AND 3

3 articles were found searching EconLIT and NHS EED

9.10.5 **Details of any additional searches (for example, searches of company databases [include a description of each database]).**

No further searches were undertaken.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

As no cost-effectiveness were identified this section is redundant.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 **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
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Medline

Embase

Medline (R) In-Process

Embase Alert (EMBA)

Econ LIT

NHS EED

Medline (MEYY), Embase (EMYY) and Medline in Process (MEIP) were searched using Dialogue Data-Star. NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website. ECONLIT was searched via the American Economic Association (AEA) website.

9.12.2 **The date on which the search was conducted.**

Datastar - Wednesday, 16th November 2011

ECONLIT and NHS EED – 2nd December 2011

9.12.3 **The date span of the search.**

1993 – 16 November 2011

1993 – 2 December 2011

9.12.4 **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).**

Table 47: Embase search for utility studies

No.	Database	Search term	Info added since	Results
1	EMYY	HEALTH ADJ RELATED NEAR QUALITY ADJ OF ADJ LIFE	unrestricted	51
2	EMYY	QUALITY-ADJUSTED-LIFE-YEAR OR QALY$2 OR QALIES	unrestricted	8413
4	EMYY	FACT-B OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	unrestricted	1705
5	EMYY	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	unrestricted	1092
6	EMYY	TTO OR TIME ADJ TRADE ADJ OFF OR SG OR STANDARD ADJ GAMBLE	unrestricted	27302
7	EMYY	1 OR 2 OR 4 OR 5 OR 6	unrestricted	37373
8	EMYY	breast ADJ cancer	unrestricted	176347
11	EMYY	BREAST-CANCER#.DE.	unrestricted	163449
12	EMYY	8 OR 11	unrestricted	198152
13	EMYY	metastatic ADJ breast ADJ cancer	unrestricted	7082
14	EMYY	advanced ADJ breast ADJ cancer	unrestricted	4409
15	EMYY	13 OR 14	unrestricted	10593
16	EMYY	7 AND 12 AND 15	unrestricted	88

Table 48: Embase Alert search for utility studies

No.	Database	Search term	Info added since	Results
1	EMBA	HEALTH ADJ RELATED NEAR QUALITY ADJ OF ADJ LIFE	unrestricted	80
2	EMBA	QUALITY-ADJUSTED-LIFE-YEAR OR QALY$2 OR QALIES	unrestricted	88
3	EMBA	FACT-B OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	unrestricted	68
4	EMBA	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	unrestricted	15
5	EMBA	TTO OR TIME ADJ TRADE ADJ OFF OR SG OR STANDARD ADJ GAMBLE	unrestricted	460
6	EMBA	1 OR 2 OR 3 OR 4 OR 5	unrestricted	670
7	EMBA	breast ADJ cancer	unrestricted	1730
8	EMBA	metastatic ADJ breast ADJ cancer	unrestricted	99
9	EMBA	advanced ADJ breast ADJ cancer	unrestricted	36
10	EMBA	8 OR 9	unrestricted	122
11	EMBA	6 AND 7 AND 10	unrestricted	1

Table 49: Medline search for utility studies

No.	Database	Search term	Info added since	Results
1	MEYY	HEALTH ADJ RELATED NEAR QUALITY ADJ OF ADJ LIFE	unrestricted	0
2	MEYY	QUALITY-ADJUSTED-LIFE-YEAR OR QALY$2 OR QALIES	unrestricted	6709
3	MEYY	FACT-B OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	unrestricted	1517
4	MEYY	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	unrestricted	1049
5	MEYY	TTO OR TIME ADJ TRADE ADJ OFF OR SG OR STANDARD ADJ GAMBLE	unrestricted	14324
6	MEYY	1 OR 2 OR 3 OR 4 OR 5	unrestricted	22423
7	MEYY	breast ADJ cancer	unrestricted	122552
8	MEYY	BREAST-NEOPLASMS#.DE.	unrestricted	130530
9	MEYY	7 OR 8	unrestricted	163457
10	MEYY	metastatic ADJ breast ADJ cancer	unrestricted	6237
11	MEYY	advanced ADJ breast ADJ cancer	unrestricted	3917
12	MEYY	10 OR 11	unrestricted	9346
14	MEYY	6 AND 9 AND 12	unrestricted	63

Table 50: Medline in Process search for utility studies

No.	Database	Search term	Info added since	Results
1	MEIP	HEALTH ADJ RELATED NEAR QUALITY ADJ OF ADJ LIFE	unrestricted	0
2	MEIP	QUALITY-ADJUSTED-LIFE-YEAR OR QALY$2 OR QALIES	unrestricted	226
4	MEIP	FACT-B OR SF-36 OR SF-12 OR EQ-5D OR EQ-5D-5L OR EUROQOL	unrestricted	98
5	MEIP	UTILITY ADJ VALUES OR UTILITY ADJ SCORES	unrestricted	61
6	MEIP	TTO OR TIME ADJ TRADE ADJ OFF OR SG OR STANDARD ADJ GAMBLE	unrestricted	619
7	MEIP	1 OR 2 OR 4 OR 5 OR 6	unrestricted	956
8	MEIP	breast ADJ cancer	unrestricted	4693
9	MEIP	metastatic ADJ breast ADJ cancer	unrestricted	268
10	MEIP	advanced ADJ breast ADJ cancer	unrestricted	100
11	MEIP	9 OR 10	unrestricted	348
12	MEIP	7 AND 8 AND 11	unrestricted	1

NHS EED and ECON LIT were search on 02/12/11 with the following strategy:

Quality adjusted life year or QALY or Qalies or EQ-5D or EQ-5D-5L or Euroqol or Time trade off or Standard Gamble or Utility value or Utility Score

Breast Cancer – Title only

Advanced or Metastatic – Title only

Utility – Title only

1 and 2 and 3 and 4

7 articles were found from NHS EED and ECONLIT.

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

9.12.6 The inclusion and exclusion criteria.

The Exclusion Criteria:

The article abstracts were read and excluded sequentially according to the criteria below:

Table 51: Exclusion criteria for utility studies

Is the paper in English?	No – Exclude
Does the abstract mention one or more utility terms (Quality of Life, HRQoL, Utility Values, or Utility Scores)	No – Exclude
Is the disease area metastatic or advanced breast cancer?	No – Exclude
Is the paper a literature review of existing utility scores used in metastatic breast cancer?	Yes – Exclude
Once a record has made it to here, it is retrieved and read in entirety and assessed against the following criteria:	
Does it derive utility values directly?	No – Exclude

Are utility values derived from the perspective of the general public?	No – Exclude
Are Time Trade Off or Standard Gamble methods of elicitation used to derive utility scores?	No – Exclude
Are utilities derived appropriate for modelling metastatic oncology health states such as PFS and PD?	No – Exclude

9.12.7 **The data abstraction strategy.**

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 **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
- NHS EED
- EconLIT.

Medline

Embase

Medline (R) In-Process

Embase Alert (EMBA)

Econ LIT

NHS EED

Medline (MEYY), Embase (EMYY) and Medline in Process (MEIP) were searched using Dialogue Data-Star. NHS EED was searched using the University of York's 'Centre for Reviews and Dissemination' (CRD) website. ECONLIT was searched via the American Economic Association (AEA) website.

Datastar - Wednesday, 16th November 2011

ECONLIT and NHS EED - 2nd December 2011

9.13.2 **The date span of the search.**

Datastar 1993 - 16 November 2011

ECONLIT and NHS EED - 1993 - 2 December 2011

9.13.3 **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).**

Table 52: Embase search for cost studies

No.	Database	Search term	Info added since	Results
1	EMYY	SOCIOECONOMICS OR COST ADJ BENEFIT ADJ ANALYSIS OR COST ADJ EFFECTIVENESS ADJ ANALYSIS OR COST ADJ OF ADJ ILLNESS OR COST ADJ CONTROL OR ECONOMIC ADJ ASPECT OR FINANCIAL ADJ MANAGEMENT OR HEALTH ADJ CARE ADJ COST OR HEALTH ADJ CARE ADJ FINANCING OR HEALTH ADJ ECONOMICS ADJ HOSPITAL ADJ COST OR (FISCAL OR FINANCIAL OR FINANCE OR FUNDING).TW. OR COST ADJ MINIMIZATION ADJ ANALYSIS OR (COST ADJ ESTIMATE$).MP. OR (COST ADJ VARIABLE$).MP. OR (UNIT ADJ COST$).MP.	unrestricted	421713
2	EMYY	RESOURCE ADJ UTILISATION OR NHS ADJ COST$1	unrestricted	4812
3	EMYY	1 OR 2	unrestricted	424415
4	EMYY	breast ADJ cancer	unrestricted	176347
5	EMYY	BREAST-CANCER#.DE.	unrestricted	163449
6	EMYY	4 OR 5	unrestricted	198152
7	EMYY	metastatic ADJ breast ADJ cancer	unrestricted	7082
8	EMYY	advanced ADJ breast ADJ cancer	unrestricted	4409
9	EMYY	7 OR 8	unrestricted	10593
10	EMYY	ENGLAND OR WALES OR UNITED ADJ KINGOM OR UK	unrestricted	3281560
11	EMYY	3 AND 6 AND 9 AND 10	unrestricted	138

Table 53: Embase Alert search for cost studies

No.	Database	Search term	Info added since	Results
1	EMBA	SOCIOECONOMICS OR COST ADJ BENEFIT ADJ ANALYSIS OR COST ADJ EFFECTIVENESS ADJ ANALYSIS OR COST ADJ OF ADJ ILLNESS OR COST ADJ CONTROL OR ECONOMIC ADJ ASPECT OR FINANCIAL ADJ MANAGEMENT OR HEALTH ADJ CARE ADJ COST OR HEALTH ADJ CARE ADJ FINANCING OR HEALTH ADJ ECONOMICS ADJ HOSPITAL ADJ COST OR (FISCAL OR FINANCIAL OR FINANCE OR FUNDING).TW. OR COST ADJ MINIMIZATION ADJ ANALYSIS OR (COST ADJ ESTIMATE$).MP. OR (COST ADJ VARIABLE$).MP. OR (UNIT ADJ COST$).MP.	unrestricted	1336
2	EMBA	RESOURCE ADJ UTILISATION OR NHS ADJ COST$1	unrestricted	52
3	EMBA	1 OR 2	unrestricted	1380
4	EMBA	breast ADJ cancer	unrestricted	1730
5	EMBA	metastatic ADJ breast ADJ cancer	unrestricted	99
6	EMBA	advanced ADJ breast ADJ cancer	unrestricted	36
7	EMBA	5 OR 6	unrestricted	122
8	EMBA	ENGLAND OR WALES OR UNITED ADJ KINGOM OR UK	unrestricted	33007
9	EMBA	3 AND 4 AND 7 AND 8	unrestricted	0

Table 54: Medline search for cost studies

No.	Database	Search term	Info added since	Results
1	MEYY	ECONOMICS OR COSTS AND COST ADJ ANALYSIS OR COST ADJ ALLOCATION OR COST-BENEFIT ADJ ANALYSIS OR COST ADJ CONTROL OR COST ADJ SAVINGS OR COST ADJ OF ADJ ILLNESS OR COST ADJ SHARING OR DEDUCTIBLES AND COINSURANCE OR MEDICAL ADJ SAVINGS ADJ ACCOUNTS OR HEALTH ADJ CARE ADJ COSTS OR DIRECT ADJ SERVICE ADJ COSTS OR DRUG ADJ COSTS OR EMPLOYER ADJ HEALTH ADJ COSTS OR HOSPITAL ADJ COSTS OR HEALTH ADJ EXPENDITURES OR CAPITAL ADJ EXPENDITURES OR VALUE ADJ OF ADJ LIFE	unrestricted	337450
2	MEYY	ECONOMICS AND HOSPITAL OR ECONOMICS AND MEDICAL OR ECONOMICS AND NURSING OR ECONOMICS AND PHARMACEUTICAL OR FEES AND CHARGES OR BUDGETS OR (LOW ADJ COST).MP. OR (HIGH ADJ COST).MP. OR (HEALTH ADJ CARE ADJ COST$).MP. OR FISCAL OR FUNDING OR FINANCIAL OR FINANCE OR (COST ADJ ESTIMATE$).MP. OR (COST ADJ VARIABLE).MP. OR (UNIT ADJ COST$).MP. OR ECONOMIC$ OR PHARMACOECONOMIC$ OR PRICE$ OR PRICING	unrestricted	411311
3	MEYY	RESOURCE ADJ UTILISATION OR NHS ADJ COST$1	unrestricted	4726
4	MEYY	breast ADJ cancer	unrestricted	122552
5	MEYY	BREAST-NEOPLASMS#.DE.	unrestricted	130530
6	MEYY	1 OR 2 OR 3	unrestricted	435611
7	MEYY	4 OR 5	unrestricted	163457
8	MEYY	metastatic ADJ breast ADJ cancer	unrestricted	6237
9	MEYY	advanced ADJ breast ADJ cancer	unrestricted	3917
10	MEYY	8 OR 9	unrestricted	9346
11	MEYY	ENGLAND OR WALES OR UNITED ADJ KINGOM OR UK	unrestricted	2700151
12	MEYY	6 AND 7 AND 10 AND 11	unrestricted	111

Table 55: Medline in Process search for cost studies

No.	Database	Search term	Info added since	Results
1	MEIP	ECONOMICS OR COSTS AND COST ADJ ANALYSIS OR COST ADJ ALLOCATION OR COST-BENEFIT ADJ ANALYSIS OR COST ADJ CONTROL OR COST ADJ SAVINGS OR COST ADJ OF ADJ ILLNESS OR COST ADJ SHARING OR DEDUCTIBLES AND COINSURANCE OR MEDICAL ADJ SAVINGS ADJ ACCOUNTS OR HEALTH ADJ CARE ADJ COSTS OR DIRECT ADJ SERVICE ADJ COSTS OR DRUG ADJ COSTS OR EMPLOYER ADJ HEALTH ADJ COSTS OR HOSPITAL ADJ COSTS OR HEALTH ADJ EXPENDITURES OR CAPITAL ADJ EXPENDITURES OR VALUE ADJ OF ADJ LIFE	unrestricted	4811
2	MEIP	ECONOMICS AND HOSPITAL OR ECONOMICS AND MEDICAL OR ECONOMICS AND NURSING OR ECONOMICS AND PHARMACEUTICAL OR FEES AND CHARGES OR BUDGETS OR (LOW ADJ COST).MP. OR (HIGH ADJ COST).MP. OR (HEALTH ADJ CARE ADJ COST$).MP. OR FISCAL OR FUNDING OR FINANCIAL OR FINANCE OR (COST ADJ ESTIMATE$).MP. OR (COST ADJ VARIABLE).MP. OR (UNIT ADJ COST$).MP. OR ECONOMIC$ OR PHARMACOECONOMIC$ OR PRICE$ OR PRICING	unrestricted	9511
3	MEIP	RESOURCE ADJ UTILISATION OR NHS ADJ COST$1	unrestricted	217
4	MEIP	1 OR 2 OR 3	unrestricted	10081
5	MEIP	breast ADJ cancer	unrestricted	4693
6	MEIP	metastatic ADJ breast ADJ cancer	unrestricted	268
7	MEIP	advanced ADJ breast ADJ cancer	unrestricted	100
8	MEIP	6 OR 7	unrestricted	348
9	MEIP	ENGLAND OR WALES OR UNITED ADJ KINGOM OR UK	unrestricted	85990
10	MEIP	4 AND 5 AND 8 AND 9	unrestricted	4

ECONLIT and NHS EED

Resource utilisation or NHS reference costs or Cost analysis

Breast Cancer – Title only

Advanced or Metastatic – Title only

1 and 2 and 3.

11 articles were found from having searched EconLIT and NHS EED

9.13.4 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

9.13.5 The inclusion and exclusion criteria.

Table 56: Exclusion criteria for cost studies

Is the paper in English?	No – Exclude
Does the abstract mention one or more cost terms (Costs, Resources, Economics)?	No – Exclude
Do costs mentioned apply to the United Kingdom?	No – Exclude
Is the disease area metastatic or advanced breast cancer?	No – Exclude
Is the paper a literature review of existing costs used in metastatic breast cancer?	Yes - Exclude
Once a record has made it to here, it is retrieved and read in entirety and included if the final exclusion 2 exclusions do not apply:	
Are costs derived directly from a large scale study (>100)?	No – Exclude
Is the study less than 5 years old?	No – Exclude

9.13.6 The data abstraction strategy.

Two individuals extracted articles as per the inclusion and exclusion criteria above. All search terms and inclusion and exclusion criteria were agreed upon before the search was conducted. After independently going through the articles, any disputes over including or excluding articles were discussed and reconciled by the two reviewers. All articles that could not be excluded were included in the review of relevant articles to help inform the economic model.