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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA)

Bevacizumab in combination with taxanes for the treatment of HER2-negative 1st line metastatic breast cancer

Roche Submission to the
National Institute for Health and Clinical Excellence
Submitted: 8th March 2010

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Section A

1 Description of technology under assessment

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

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

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

Yes.

EMEA approval for bevacizumab plus paclitaxel received 28th March 2007.

EMEA approval for bevacizumab plus paclitaxel or docetaxel received 23rd July 2009.

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

- *Colorectal:* Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum.

- *Breast:* Avastin in combination with paclitaxel or docetaxel is indicated for first-line treatment of patients with metastatic breast cancer.

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

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

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

Currently there is minimal use in the NHS.

No clinical trials are currently recruiting first-line metastatic HER2- patients in the UK. In UK private practice, the technology is currently used in about 35% of eligible patients.

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

Yes:

EMEA: A centralised licence (EMEA licence) has been received for Avastin thus the product is licensed for use in all member states of the EU.

FDA: The FDA has also approved the use of Avastin in the above indications, plus:-

- In Glioblastoma, as a single agent for patients with progressive disease following prior therapy.

However, in the USA, Avastin is so far indicated only with paclitaxel, for treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer.

Other licences: Avastin is licensed also in most major countries of the world and is reimbursed and used extensively in those countries.

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

No other HTA is currently scheduled in the UK for this specific indication.

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

Vials containing either 100 mg of bevacizumab in 4 ml or 400 mg in 16 ml. Pack size consists of 1 vial.

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

For metastatic breast cancer the recommended dose of Avastin is 10 mg/kg of body weight given once every 2 weeks or 15 mg/kg of body weight given once every 3 weeks as an intravenous infusion.

It is recommended that treatment with Avastin be continued until progression of the underlying disease. In the Phase III registration studies, the median progression-free survival in Avastin-treated patients was in excess of 10 months.

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

100mg/4ml vial - £242.66
400mg/16ml vial - £924.40

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

Bevacizumab must be administered under the supervision of a physician experienced in the use of antineoplastic medicinal products. It will be administered in the outpatient setting.

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

No additional tests are required to select patients for the administration of bevacizumab. Treatment with bevacizumab should continue until disease progression, which will be determined in the usual manner for metastatic breast cancer patients. A small amount of additional resource will be required for the administration of bevacizumab alongside the patient's routine taxane therapy. There will be minimal monitoring, in addition to that required for taxane therapy, to detect the most common side effects of bevacizumab.

2 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission
Population	People with untreated metastatic HER2-negative breast cancer for whom anthracyclines are not appropriate	This population is covered in this submission. However, the economic analysis is based on the ITT population for the pivotal trial in order to maintain randomisation. The E2100 study included 15 (2.1%) patients with HER2-positive disease and 57 (7.9%) patients with HER2 status unknown.
Intervention	Bevacizumab in combination with a taxane	This is the intervention that is covered in this submission
Comparator(s)	Bevacizumab in combination with paclitaxel and bevacizumab in combination with docetaxel should be compared with each other. In addition, the interventions should be compared with the following: • Docetaxel monotherapy • Paclitaxel monotherapy • Paclitaxel in combination with gemcitabine	These comparisons are covered in this submission. Indirect comparisons were necessary for this analysis as head to head trials are not available for all comparisons requested.

	Final scope issued by NICE	Decision problem addressed in the submission Continued…
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rates • adverse effects of treatment • health-related quality of life	These outcomes are covered in this submission
Economic Analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulated 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.	The NICE reference case is followed in this submission.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation	There are equality issues in the provision of care for metastatic breast cancer and these are addressed in this submission.

Section B

3 Executive Summary

- This submission concerns bevacizumab, Avastin®, a recombinant humanised anti-VEGF antibody. Bevacizumab received a UK marketing authorisation in January 2005 for metastatic colorectal cancer, in April 2007 for metastatic breast cancer and in August 2007 for metastatic non-small cell lung cancer. Bevacizumab binds and inactivates human VEGF, thereby inhibiting angiogenesis, which is a process vital to the survival and growth of tumours (Section 4.2, 4.3).

  Bevacizumab is supplied as a 25 mg/ml concentrate for solution for infusion. Vials containing 100 mg or 400 mg bevacizumab are supplied in single vial packs. For administration in metastatic breast cancer, bevacizumab is diluted in 100 ml sodium chloride solution for injection, to give a dose of 10 mg/kg body weight q2w or 15 mg/kg q3w (Avastin® [bevacizumab], Summary of Product Characteristics [SPC]). Acquisition cost, 100-mg vial = £242.66; 400-mg vial = £924.40

Licensed Indications

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

  Avastin (bevacizumab) in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of patients with metastatic carcinoma of the colon or rectum. Bevacizumab, in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology.

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

Bevacizumab is not recommended for use in children and adolescents due to a lack of data on safety and efficacy (Avastin® bevacizumab, SPC).

- It is recommended that treatment with bevacizumab be continued until progression of the underlying disease. In patients treated with bevacizumab plus paclitaxel or docetaxel for metastatic breast cancer and who discontinue the taxane prior to progression, single-agent bevacizumab therapy should be continued until disease progression. (Avastin® [bevacizumab] SPC).

- In metastatic breast cancer, bevacizumab plus paclitaxel was compared with paclitaxel alone,one of the gold-standard therapies for metastatic patients who have previously received anthracycline therapy in the adjuvant setting (Section 4.1).

- For reasons associated with dosing in routine NHS clinical practice and the cost-effectiveness profile, this submission focuses on the clinical and cost-effectiveness of bevacizumab in combination with paclitaxel. The cost-effectiveness of bevacizumab in combination with docetaxel is discussed briefly (see last section of the Executive Summary below).

Clinical Effectiveness

Study E2100: an open-label, active controlled, phase III study in which 722 patients were randomised to receive treatment with either bevacizumab plus paclitaxel or paclitaxel monotherapy.

The pivotal randomised controlled trial (RCT), study E2100, demonstrated that the addition of bevacizumab to paclitaxel chemotherapy provides substantial benefit to patients with metastatic breast cancer who had not previously received chemotherapy for advanced disease. This was shown by statistically and clinically significant increases in median progression-free survival (PFS), from 5.8 months to 11.3 months and in objective response rate from 22.2% to 49.8% with bevacizumab plus paclitaxel versus paclitaxel alone. The relative risk of progression was reduced by more than half (Hazard Ratio 0.48) with the combination therapy versus paclitaxel

alone. The median overall survival was 1.7 months longer (not statistically significant) with bevacizumab plus paclitaxel (26.5 months) than with paclitaxel alone (24.8 months). However, overall survival at 1 year was significantly higher with paclitaxel plus bevacizumab (81.4%) vs paclitaxel alone (74.0%) This represents a 10% relative improvement in overall survival at 1 year (p=0.017) with bevacizumab (Section 6.4).

Data from two additional Phase III RCTs, the AVADO and the RIBBON-1 studies, are not presented in this submission because they are considered to have limited relevance. In the AVADO study all patients were given docetaxel at a dose of 100 mg/m^2 q3w for up to nine cycles. This dosing regimen is not representative of routine NHS clinical practice, where clinicians generally treat first-line metastatic breast cancer patients with docetaxel 75mg/m^2 q3w for a maximum of 6, or in exceptional cases 8, cycles.

In the RIBBON-1 study, patients were entered into one of two cohorts, for treatment with capecitabine or taxane/anthracycline. The complete taxane/anthracycline cohort had 90% power to detect a HR of 0.7 for PFS, based on a sample size of 600 patients. The study was not powered to provide any individual endpoints for the 180 patients treated with docetaxel plus bevacizumab or versus placebo.

Cost Effectiveness

- The economic evaluation utilises the key outcomes of the E2100 clinical trial and is designed for the purposes of estimating lifetime NHS costs and QALYs for bevacizumab in combination with paclitaxel and three relevant comparators (paclitaxel, docetaxel, and gemcitabine in combination with paclitaxel). The model conforms to the reference case as described in NICE's Guidance to the Methods of Technology Appraisal with the exception of a focus exclusively on NHS list price. Instead, the average PASA price for paclitaxel was used as directed by NICE during the decision problem meeting due to the precedent set during the Gemcitabnie STA.. Also, the 10g bevacizumab capping scheme, which has been available to any NHS

or private patient that receives bevacizumab over the past several years, will be considered.

The economic model developed was a three-state Markov model, where patients are assumed to be within one of three possible discrete health states at any given time; “progression-free survival”, “progressed” or “death”. Lifetime progression free survival was estimated from an extrapolation of the PFS curves from the E2100 trial for the bevacizumab/paclitaxel and paclitaxel arms. The efficacy of docetaxel and gemcitabine/paclitaxel were based upon assumptions reflecting UK clinical practice and supported by an indirect treatment comparison and evidence from the early breast cancer setting. A Markov process was constructed to model the transition from the progressed health state to death irrespective of 1st line treatment choice. Remaining model inputs were taken from the published literature where possible and supplemented with UK expert medical opinion where necessary.

According to the NICE clinical guideline (CG81) UK standard of care for first line metastatic breast cancer is docetaxel, this is reflected in the latest market research data available to Roche, suggesting docetaxel is the taxane of choice in 81% of patients. The cost per QALY for bevacizumab/paclitaxel compared to the most relevant comparator of docetaxel is estimated to be £57,753. One-way and probabilistic sensitivity analysis were performed to test the robustness of the base case cost-effectiveness estimates.

The base case results suggest that bevacizumab in combination with paclitaxel has an ICER greater than £50,000.. This is despite a median doubling in progression-free survival and also considering the combination of bevacizumab with a relatively inexpensive taxane (paclitaxel at PASA price) compared to a substantially more expensive taxane (docetaxel). It can therefore be inferred that bevacizumab in combination with docetaxel (the expensive taxane) is highly unlikely to provide a more cost-effective outcome than the analysis presented in this submission. It is therefore clear, without the need of a full economic analysis, that bevacizumab in combination with docetaxel is not cost-effective by UK standards.

4 Context

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

According to the Office for National Statistics (2008), 44,400 new cases of female breast cancer were diagnosed in England during 2004. There were 12,300 female deaths from breast cancer in England in 2004. Most women developing breast cancer are post-menopausal, with incidence increasing with advancing age. Once adjustment is made for the age of the local population, incidence rates are generally consistent throughout the UK (ONS 2008).

Although mortality from the disease has dropped in recent years (ONS 2008), survival in the UK after diagnosis with breast cancer is still lower than that in other European countries, with the exception of former Eastern bloc countries (Berrino *et al.* 2007; Ferlay 2006). Addressing this difference has been made a priority in the government's National Cancer Plan (Department of Health 2000).

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 and to also affect 30-40% of patients initially diagnosed with early or localised breast cancer confined to the breast and its draining lymph nodes (O'Shaughnessy 2005; Burstein *et al.* 2008; NICE CG81 2009).

The median time from diagnosis with metastatic disease to death has been reported to be about 2 years (IARC 2003), but such figures hide considerable heterogeneity. For example, post-menopausal women with tumours bearing large numbers of both oestrogen and progesterone receptors (ER, PgR) typically have disease that follows a relatively indolent course and these patients may survive for a prolonged period of time

(Muss *et al.* 1987; Ravdin *et al.* 1992; Anderson *et al.* 2005). Other patients have more aggressive forms of the disease, which are associated with a much higher risk of early relapse and short overall survival. For example, the amplification of the HER-2/*neu* gene that is found in 15-20% of breast cancers is associated with particularly aggressive disease and a reduction in median survival of up to 50% (Slamon *et al.* 1987; Ibrahim *et al.* 2008). Patients with breast tumours which lack not only hormonal receptors (ER, PgR) but also HER2, the so-called triple-negative tumours, also have a very poor prognosis, similar to that of HER2-positive breast cancer in the absence of HER2-targeted therapy (Dent *et al.* 2007, Dawood *et al.* 2009).

Other factors which contribute to a high risk of early relapse and death are the presence of positive lymph nodes or a large tumour at the time of diagnosis and a high histological Grade. For example, the 5-year breast cancer specific mortality rate is 41% for patients with 4 or more positive nodes at presentation, compared with 0.8% for patients with node-negative disease (NCCN Guidelines 2006). High tumour Grade provides a poor prognosis regardless of tumour size; the 2-year overall survival of women with tumours ≤1 cm diameter was 100% with Grade 1 tumours, but less than 85% for Grade 3 tumours (Kollias *et al.* 1999). For tumours of all sizes, 10-year overall survival was 91% for Grade 1 and 68% for Grade 3 disease (Blamey *et al.* 2010). The percentage of Grade 3 tumours at presentation also rises with increasing size, from 20% for tumours of 1-5 mm diameter, to 55% for 2-3 cm and 61% for 3-5 cm tumours respectively (Kolias *et al.* 1999*).* This may be one reason for the significantly worse prognosis of patients presenting with large tumours, with 10-year overall survival of 88% for tumours <1 cm compared with 53% for tumours 4-5 cm at presentation (Blamey *et al.* 2010).

4.1.1 Current Management of Breast Cancer

4.1.1.1 Early Breast Cancer

As stated above, 90-95% of women with breast cancer present with overt disease confined to the breast and its draining lymph nodes (early breast cancer). Such tumours are suitable targets for potentially curative surgery. Unfortunately, despite such

treatment, a significant proportion of women with operable early breast cancer subsequently relapse, usually with metastatic disease at sites remote from the initially affected breast. It is assumed that these relapses arise from cells that were shed from the primary tumour before surgical excision and this assumption led to trials of adjuvant treatment to eradicate such 'occult' metastases. Adjuvant treatment is therapy delivered after apparently successful surgery, with the aim of reducing the risk of relapse. There have been many large trials of adjuvant therapies, the results of which form the basis of an on-going meta-analysis project conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).

The most recent update from EBCTCG (EBCTCG 2005) reviewed the use of both cytotoxic and hormonal treatments in the adjuvant setting. It included data from 49,359 women (and 16,784 deaths) receiving adjuvant chemotherapy with combinations of cytotoxic drugs (polychemotherapy) who entered randomised studies commenced before 1990. This report once again gave solid support to the concept that adjuvant polychemotherapy results in a clinically significant reduction in mortality for all patients, regardless of age. The 2005 report confirmed that anthracycline-containing regimens (with doxorubicin or epirubicin) gave a reduction in the annual breast cancer death rate of about 38% for women under 50 years and of about 20% for older women. Anthracycline-containing regimens were also shown to be significantly more effective than the older CMF (cyclophosphamide, methotrexate and 5-fluorouracil [5-FU]) adjuvant therapy regimens (EBCTCG 2005).

More recently, a number of large clinical trials have reported on the efficacy of adding a taxane into anthracycline adjuvant therapy regimens. A meta-analysis of 13 studies in 22,903 patients showed that overall, addition of a taxane gave a 17% reduction in the risk of recurrence and a 15% reduction in the risk of death (De Laurentiis *et al.* 2008). The majority of patients in the meta-analysis were lymph node positive.

The value of adjuvant chemotherapy in early breast cancer has been recognised in the UK for nearly two decades. One change in recent years has been the switch from adjuvant chemotherapy based on CMF to anthracycline-based regimens containing

epirubicin or doxorubicin, which are now considered the gold-standard for adjuvant chemotherapy (Bergh *et al.* 2001, EBCTCG 2005; ESMO 2008). Thus it is now unusual for a fit patient with early breast cancer not to receive adjuvant chemotherapy which includes an anthracyline. Also, in accordance with the NICE recommendations for use of docetaxel in node-positive patients (TA109 and CG80), most patients presenting with node-positive early breast cancer in the UK now receive taxane therapy in the adjuvant setting. In current clinical practice, the recognition of the poor prognosis associated with high tumour Grade, large tumour at presentation and triple-negative disease means that some of these patients also receive taxane adjuvant therapy, even if node-negative.

4.1.1.2 Metastatic Disease

The group of women who present with disease that has spread outside of the breast and its draining lymph nodes, and also those who relapse after treatment for early breast cancer, have systemic disease which is usually incurable. However, systemic treatment with either hormonal or other targeted therapy, or cytotoxic chemotherapy has been shown to extend survival and palliate the symptoms of the disease.

Treatment Objectives

In general terms, the treatment of metastatic breast cancer requires sequential use of a series of treatments which induce remission, but from which the disease relapses after a period of time. Different treatments are usually introduced each time therapy is restarted, because there is an assumption that the disease has regrown from cells which were resistant to previously administered treatments. Because response rates and the duration of response decline with each successive treatment (Jones 2008; Wood *et al.* 2005; Burstein *et al.* 2008) the patient's prospect of long-term survival falls each time the disease recurs. Cancer survivors who have a recurrence 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 survivors was found to be the fear of disease progression (Herschbach 2004). For all the above reasons, the major objective of each successive line of therapy is to maintain disease remission for as long as possible.

Existing treatments used in the first-line metastatic setting are capable of prolonging both disease-free and overall survival. There are currently no new therapies in prospect which, when used as a monotherapy, can significantly improve on the efficacy of existing agents in first-line therapy. Advances in this treatment setting are being made by the addition of new therapies to the existing gold-standard agents. Such advances are generally marked by an increase in the proportion of patients responding to therapy and a prolongation of the time these patients remain free of disease. However, because current treatment pathways for metastatic breast cancer incorporate many active agents delivered in a sequential fashion, it is often very difficult to demonstrate a statistically significant overall survival advantage for a therapy used in the first-line setting.

Hormonal Treatment of Metastatic Breast Cancer

For the approximately 60% of women whose tumours are oestrogen receptor positive, hormonal therapy is generally the treatment of first choice (Anderson *et al.* 2005; Burstein *et al.* 2008; NICE CG81 2009). Around two-thirds of patients have been shown to respond to first-line hormonal therapy and these agents are generally well tolerated. For patients who initially respond to hormonal manipulation, their eventual relapse (typically after 12-18 months) can be treated with second- and third-line therapies, but ultimately all surviving patients become resistant to endocrine therapy. At this point they are likely to be assessed with a view to instituting cytotoxic chemotherapy (Burstein *et al.* 2008).

First-Line Cytotoxic Treatment for Metastatic Disease

For women whose tumours lack hormone receptors or are fast-growing and affect vital organs, endocrine therapy is not appropriate so the first treatment given for metastatic disease is generally cytotoxic chemotherapy. Thus, most women with metastatic disease ultimately become candidates for systemic chemotherapy.

Chemotherapy for metastatic breast cancer was introduced in the 1960s on the basis that it induced tumour regression and improved the sense of well being in a proportion of patients. Prospective randomised controlled trials comparing the outcomes in chemotherapy-treated patients with untreated groups were not considered necessary or

appropriate. However, a variety of indirect evidence has been collected which demonstrates the benefits of systemic chemotherapy in metastatic breast cancer. This is described in a large systematic review carried out by The Swedish Council of Technology Assessment in Health Care (SBU) (Bergh *et al.* 2001).

This review reached the following conclusions:

- The median survival gain associated with non-anthracycline based chemotherapy was about 6-9 months.
- Survival improved significantly upon addition of an anthracycline drug to the chemotherapy regimen.
- Anthracycline-based chemotherapy should be standard first-line therapy, for eligible patients.
- Cytotoxic chemotherapy is associated with improved quality of life, despite having significant toxicity.

Reassuringly, the early view of clinicians that tumour regression was of self-evident benefit to patients has since been verified in studies which show that objective measures of quality of life and patient well-being correlate with tumour shrinkage in breast cancer (Geels *et al.* 2000; Baum *et al.* 1980; Coates *et al.* 1987; Ramirez *et al.* 1998).

Choice of Cytotoxic therapy for Treatment of Metastatic Disease

Because development of cytotoxic drug resistance is common, once used, individual chemotherapeutic drugs are seldom re-used to treat the same patient at relapse. Additionally, because anthracyclines have a cumulative cardiotoxicity, re-treatment with such drugs is often ruled out on the basis of the previous dose received. Thus although the anthracyclines have been regarded as the standard first-line therapy, many of the women who develop metastatic breast cancer in the UK are now unsuitable for anthracycline therapy because of the widespread use of these agents in the adjuvant setting. For patients given adjuvant docetaxel, rechallenge with a taxane in the metastatic setting may be delayed until 12-18 months after the completion of adjuvant therapy and paclitaxel may be the agent of choice for such patients.

The 2009 National Institute for Clinical Excellence (NICE) Clinical Guideline (CG)81, 'Advanced breast cancer: diagnosis and treatment', recommends that for patients with advanced breast cancer who are not suitable for anthracyclines (patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated), systemic chemotherapy should be offered in the following sequence:- single-agent docetaxel first-line, followed by single-agent vinorelbine or capecitabine, followed by single-agent capecitabine or vinorelbine. This recommendation was based on the findings of a health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens. However, the GDG acknowledged that the existence of price discounts for paclitaxel can significantly alter the cost effectiveness of the sequences examined in the analysis (NICE CG81 2009).

NICE has twice reviewed the evidence for taxanes in the treatment of breast cancer which has relapsed after anthracycline-based chemotherapy (NICE TA30 2001, NICE CG81 2009). NICE has concluded that both paclitaxel and docetaxel produce an objective anti-tumour response, both improve progression-free survival (PFS) and there is evidence that docetaxel, in particular, extends overall survival. NICE recommended that both taxanes should be made available for use by the NHS, thus recognising the importance of patient and clinician choice in this area (NICE TA30 2001).

Studies of taxane monotherapy

The phase III randomised trials of docetaxel monotherapy (100 mg/m^2 3-weekly [q3w]) in metastatic breast cancer have shown an objective response rate between 30 and 48%, a median time to progression (TTP) of 4.5 to 6.5 months and median overall survival (OS) of 11 to 18 months (Table 1). In all but one of these studies (Rivera *et al.* 2008), more than half of the patients recruited had received previous chemotherapy for metastatic disease (i.e., not first-line patients) (Table 2).

With standard-dose 3-weekly paclitaxel monotherapy (175-200 mg/m^2 q3w) objective response rates in phase III trials have been between 25 and 34%, median TTP between 3.6 and 6.3 months and median OS was 12 to 22 months (Table 3). An increased dose, of 250 mg/m^2 q3w, raised the ORR to 44% but did not improve TTP or OS (Smith *et al.*

1999). These paclitaxel studies all appear to have included only first-line metastatic patients (Table 4). Paclitaxel has shown greater activity when given in a weekly (80-90 mg/m^2 qw) rather than a 3-weekly schedule. The weekly regimen gave a higher response rate (42% vs 27-29%) in two trials (Seidman *et al.* 2008; Verrill *et al.* 2007). In the US study (Seidman *et al.* 2008), in which treatment was continued to disease progression, there was also a longer median TTP (9.0 vs 5.0 months) and OS (24 vs 12 months) with weekly paclitaxel dosing. In the UK study (Verrill *et al.* 2007), paclitaxel qw was limited to 12 cycles (Table 4), which may in turn have limited the time to progression with weekly dosing (24 weeks). Nevertheless, these efficacy results for weekly paclitaxel compare very favourably with those obtained for 3-weekly docetaxel, albeit in a predominantly first-line population.

It is of note that none of the taxane therapy studies yet reported have included analyses of efficacy in sub-groups, such as triple-negative patients or those receiving prior adjuvant chemotherapy. The timelines for recruitment into these studies mean that few of the included patients will have received prior adjuvant taxane therapy and indeed such patients were excluded from at least two of the studies (Seidman *et al.* 2008, Verrill *et al.* 2007).

Thus the efficacy of taxane monotherapy in the treatment of metastatic breast cancer is comparable with the results for anthracycline therapy in this disease setting. However, it is difficult to determine from the available phase III data, whether the two taxanes each have similar efficacy in metastatic breast cancer. There is only a single phase III comparative trial of the two taxanes, which used 3-weekly dosing of both agents, in a population of mixed first-line and second-line patients (Jones *et al.* 2005, Table 10). In this study, docetaxel q3w was significantly more effective than paclitaxel q3w, for TTP (5.7 vs 3.6 months, Hazard Ratio (HR) 1.64, $p<0.0001$) and OS (15.4 vs 12.7 months, HR1.41, $p=0.03$). The ORR was higher, but not significantly so, with docetaxel (32 vs 25%, $p= 0.1$). This greater efficacy was, however, gained at the cost of greater toxicity; the incidence of Grade 3-4 neutropenia, infection, asthenia, oedema, stomatitis and neurosensory side effects was greater in the docetaxel arm of the study.

Because paclitaxel has been shown to be more effective when dosed qw rather than q3w, the above study does not provide a comparison of the two taxanes, each given in their most effective dosing schedule. A more recent publication compared docetaxel with paclitaxel, each drug dosed either q3w or qw, in a large (4950 patient) study in node-positive or high-risk node-negative early breast cancer patients (Sparano *et al.* 2008, Table 10). Patients received 4 cycles of doxorubicin and cyclophosphamide q3w, followed by taxane therapy for 12 weeks, given either as 4 cycles q3w, or as 12 weekly doses.

This study confirmed the observations from metastatic disease, that paclitaxel is more effective when given qw than q3w and it also confirms the superiority of docetaxel over paclitaxel in the q3w regimen. Compared with 'standard therapy' of paclitaxel q3w, there was longer disease-free survival (DFS) (HR 1.27, p=0.006) and OS (HR 1.32, p=0.01) with paclitaxel given qw. Docetaxel q3w also gave longer DFS (HR 1.23, p=0.02) than paclitaxel q3w, but OS was not significantly improved with docetaxel q3w (HR 1.13 p=0.25 versus paclitaxel q3w). Weekly docetaxel did not significantly improve either DFS or OS compared with paclitaxel q3w. This large study in early breast cancer, which compared the four most common taxane dosing regimens also clearly demonstrated that docetaxel q3w and paclitaxel qw are the most effective regimens. Paclitaxel qw gave the highest 5-year DFS and OS (81.5% and 89.7%), followed by docetaxel q3w (5-year DFS 81.2% and OS 87.3%).

In the early breast cancer study (Sparano *et al.* 2008), weekly paclitaxel was also associated with the lowest level of grade 3-4 adverse events. Twenty-eight percent of patients given paclitaxel qw recorded grade 3-4 adverse events, compared with 30% given paclitaxel q3w (p=0.32 vs paclitaxel qw), 71% given docetaxel q3w (p<0.001) and 45% given docetaxel qw (p<0.001). There is a general recognition that paclitaxel qw has a more benign toxicity profile than other taxane dosing regimens, which leads to better compliance with therapy (Perez *et al.* 2001; Green *et al.* 2005).

Overall, the good tolerability, plus the high level of efficacy demonstrated for weekly paclitaxel in both early and metastatic breast cancer, means that weekly paclitaxel is

becoming a treatment of choice for metastatic patients who may be unable to tolerate the more toxic 3-weekly docetaxel regimen.

There is a recognition that the efficacy of single-agent anthracycline or taxane therapy is only likely to be improved by combination with additional agents in metastatic breast cancer (Carrick *et al.* 2009). However, any improvement in efficacy is generally accompanied by considerably increased toxicity. NICE Clinical Guideline 81 states "consider combination therapy for patients for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity" (NICE CG81 2009).

Studies of taxanes in combination therapy

Studies of the combination of anthracyclines plus taxanes have demonstrated an increase in objective response rate, generally to the range 40-60% and a prolongation of TTP (Luck *et al.* 2000; Jassem *et al.* 2009; Biganzoli *et al.* 2002; Nabholtz *et al.* 2003; Maiorino *et al.* 2004; Fountzilas *et al.* 2004; Bonneterre *et al.* 2004; Langley *et al.* 2005; Mavroudis *et al.* 2005). However, the combination of anthracycline plus taxane is associated with incremental toxicity, including high levels of neutropenia. A phase III study in 210 patients compared doxorubicin plus docetaxel versus doxorubicin plus paclitaxel and showed no difference in PFS or objective response rate between the two arms (Cassier *et al.* 2008).

For those patients who are unable to receive anthracycline therapy in the metastatic setting, other combination therapies have shown value. Capecitabine, in combination with docetaxel in anthracycline pre-treated patients, was compared with docetaxel alone in a randomised phase III study in 511 patients (O'Shaughnessy *et al.* 2002; Miles *et al.* 2004). Compared with patients receiving docetaxel alone, those receiving capecitabine plus docetaxel had significantly better overall survival (median 11.5 vs 14.5 months, $p<0.01$), superior TTP (4.2 vs 6.1 months, $p=0.0001$) and tumour response rate (30% vs 42%, $p=0.006$). The percentage of patients experiencing grade 3 treatment-related adverse events was higher in the combination therapy group (71% vs 49% in the single-agent docetaxel arm). However, there was a slightly lower incidence of grade 4

treatment-related adverse events with combination therapy (25% vs 31%). NICE recommended that capecitabine in combination with docetaxel should be used in preference to single-agent docetaxel in people for whom anthracycline-containing regimens are unsuitable or have failed (NICE TA62 2003).

Table 1. Phase III trials of docetaxel monotherapy in mBC.

Phase III study	**Median time to progression (TTP)**		**Objective response rate (ORR)**		**Median overall survival (OS)**	
	Docetaxel q3w	*Comparator*	*Docetaxel q3w*	*Comparator*	*Docetaxel q3w*	*Comparator*
Nabholtz 1999 Docetaxel (n=203) vs mitomycin + vinblastine (n=189)	19 weeks (4.5 mo)	11 weeks (2.6 mo)	30.0%	11.6%	11.4 months	8.7 months
Chan 1999 Docetaxel (n=161) vs doxorubicin (n=165)	26 weeks (6.0 mo)	21 weeks (4.9 mo)	47.8%	33.3%	15 months	14 months
Bonneterre 2002 Docetaxel (n=86) vs 5-fluorouracil + vinorelbine (n=90)	6.5 months	5.1 months	43.0%	38.8%	16 months	15 months
Rivera 2008 Docetaxel weekly[a] (n=63) vs docetaxel q3w[b] (n=63)	5.7 months q3w	5.5 months Weekly	35.6% q3w	20.3% Weekly	18.3 months q3w	18.6 months Weekly
Nielsen 2009 Docetaxel[c] (n=151) vs GT[d] (n=155)	6.5 months	7.5 months GT	38%	44% GT	13.2 months	13.4 months GT

All patients received docetaxel 100 mg/m^2 q3w unless otherwise stated.
[a] 35 mg/m^2 d1, d8, d15 q4w for first cycle escalating to 40 mg/m^2 if tolerated;
[b] 75 mg/m^2 d1 q3w for first cycle escalating to 100 mg/m^2 if tolerated.
[c] Docetaxel 100 mg/m^2 d1 q3w;
[d] Gemcitabine 1000 mg/m^2 d1, d8 + docetaxel 75 mg/m^2 d1 q3w.
GT: Gemcitabine-docetaxel; mo: months; q3w: Every 3 weeks.

Table 2. Phase III trials of docetaxel monotherapy in mBC – dosage and patient characteristics.

Phase III study	Dosage	Median no. cycles	Median relative dose intensity	Age in years Mean (median)	ER (+) (%)	HER2 (+) (%)	Number (%) of patients with <3 metastatic sites	Previous adjuvant chemo; number (%)	Previous chemo for metastatic disease; number (%)
Nabholtz 1999 Docetaxel (n=203) vs mitomycin + vinblastine (n=189)	100 mg/m^2 q3w, max 10 cycles	6	0.94	51.0 (52.0)	NR	NR	60 (48)	51 (50)	83 (79)
Chan 1999 Docetaxel (n=161) vs doxorubicin (n=165)	100 mg/m^2 q3w, max 7 cycles	7	0.97	52.0 (52.0)	NR	NR	56 (57)	57 (51)	49 (58)
Bonneterre 2002 Docetaxel (n=86) vs 5-fluorouracil + vinorelbine (n=90)	100 mg/m^2 q3w, max 9 cycles	6	0.97	54.9 (54.55)	NR	NR	64 (62.2)	50 (58.9)	69.7 (62.2)
Rivera 2008 Docetaxel weekly (n=63) vs docetaxel q3w (n=63)	100 mg/m^2 q3w[a]; 40 mg/m^2 weekly[b]	7, qw 9.5, q3w	NR	56 (54)	48% (56%)	13% (5%)	*Median* 3.5 (3.5)	58% (63%)	31% (29%)
Nielsen 2009 Docetaxel (n=151) vs GT (n=155)	100 mg/m^2 q3w 75 mg/m^2 q3w (GT)	NR	NR	58 (58)	NR	0% (0%)	NR	NR	NR

* Docetaxel or paclitaxel given until disease progression, unacceptable toxicity or patient withdrawal. [a] 75 mg/m^2 cycle 1 escalating to 100 mg/m^2 if tolerated, q3w; [b] 35 mg/m^2 d1, d8, d15 q4w cycle 1 escalating to 40 mg/m^2 if tolerated.
NR: Not reported; Pac: Paclitaxel; q3w: Every 3 weeks.

Table 3. Phase III trials of paclitaxel monotherapy in mBC.

Phase III study	**Median PFS/TTP/TTF**		**Objective response rate (ORR)**		**Median overall survival (OS)**	
	Paclitaxel	*Comparator*	*Paclitaxel*	*Comparator*	*Paclitaxel*	*Comparator*
Bishop 1999 Paclitaxel (n=107) vs CMFP (n=102)	5.3 months	6.4 months	29.0%	35.0%	17.3 months	13.9 months
Smith 1999* 3-hr paclitaxel (n=279) vs 24-hr paclitaxel (n=284)	6.3 months	7.2 months (24-hr)	44.1%	54.4% (24-hr)	21.1 months	21.9 months (24-hr)
Paridaens 2000 Paclitaxel (n=166) vs DOX (n=165)	3.9 months	7.5 months	25.0%	41.0%	15.6 months	18.3 months
Sledge 2003 Paclitaxel (n=242) vs doxorubicin (DOX) (n=245) vs doxorubicin/ paclitaxel (AT) (n=244)	6.3 months	6.0 months DOX / 8.2 months AT	34.0%	36.0% DOX / 47.0% AT	22.5 months	19.1 months DOX / 22.4 months AT
Seidman 2008 Paclitaxel q3w (n=385) vs weekly (n=350)	5.0 months q3w	9.0 months qw	29% q3w	42% qw	12 months q3w	24 months qw
Verrill 2007 Paclitaxel (n=569)	22 weeks (5.1mo) q3w	23.9 weeks (5.6 mo) qw	27% q3w	42% qw	NA	NA
Di Leo 2008 Paclitaxel (n=288) vs paclitaxel/lapatinib (n=291)	22.9 weeks (5.3mo)	29 weeks (6.8mo)	25.3%	35.1%	87 weeks	99.1 weeks

q3w: Every 3 weeks; qw: Weekly; Paclitaxel dose 175-200 mg/m^2 q3w, or 80-90 mg/m^2 qw. Paclitaxel given q3w unless qw stated. *High-dose paclitaxel (250 mg/ m^2 q3w) TTF: Time to treatment failure; TTP: Time to progression.*

Table 4. Phase III trials of paclitaxel monotherapy in mBC – dosage and patient characteristics.

Phase III study	Dosage	Median no. cycles	Median relative dose intensity	Age in years Mean (median)	ER (+) (%)	HER2 (+) (%)	Number (%) of patients with <3 metastatic sites	Previous adjuvant chemo; number (%)	Previous chemo for metastatic disease; number (%)
Bishop 1999 Paclitaxel (n=107) vs CMFP (n=102)	200 mg/m^2 q3w, max 8 cycles	NR	NR	Pre-menopause 47 (48)	40 (37)	NR	NR	21 (32)	0 (0)
Smith 1999 3-hr paclitaxel (n=279) vs 24-hr paclitaxel (n=284)	250 mg/m^2 q3w*	6, 3-hr 7, 24-hr	NR	% <50 yrs 35.1, 3 hr 34.9, 24-hr	NR	NR	68.4 3-hr 67.6 24-hr	53.2 3-hr 52.5 24-hr	NR
Paridaens 2000 Paclitaxel (n=166) vs DOX (n=165)	200 mg/m^2 q3w, max 7 cycles	7	0.99	54 (55)	27 (24)	NR	72 (68)	32 (33)	0 (0)
Sledge 2003 Paclitaxel (n=242) vs doxorubicin (DOX) (n=245) or doxorubicin/ paclitaxel (AT) (n=244)	175 mg/m^2 q3w* 150 mg/m^2 q3w* (AT)	NR	NR	56 (DOX 58, AT 58)	47 (DOX 46, AT 44)	NR	47 (DOX 47, AT 53)	31 (DOX 31, AT 33)	0 (0)
Seidman 2008 Paclitaxel q3w (n=385) vs weekly (n=350)†	175 mg/m^2 q3w*; 80mg/m^2 qw*	NR	NR	% <50 years 25 q3w; 18 qw	66 q3w; 77 qw	NR	NR	NR	2nd line pts:- 28% q3w; 9% weekly
Verrill 2007 Paclitaxel (n=569)	175 mg/m^2 q3w, max 6 cycles; 90 mg/m^2 qw, max 12 cycles No demographic data available								
Di Leo 2008 Paclitaxel (n=288) vs paclitaxel /lapatinib (n=291)	175 mg/m^2 q3w, max 6 cycles	NR	NR	52.4 (51.3)	50 (44)	13 (17)	42 (45)	Anthra/taxane 45/7	0 (0)

*Until disease progression or unacceptable toxicity. † Patients with HER2-positive disease received trastuzumab. Patients with HER2-negative tumors were randomly assigned to receive trastuzumab or not. Anthra: Anthracycline; AT: Doxorubicin+paclitaxel; DOX: Doxorubicin; NR: Not reported; Pts: Patients; q3w:

Table 5. Phase III trial of nab-paclitaxel monotherapy in mBC.

Phase III study	Median PFS/TTP/TTF		Objective response rate (ORR)		Median overall survival (OS)	
	Nab-paclitaxel	*Paclitaxel*	*Nab-paclitaxel*	*Paclitaxel*	*Nab-paclitaxel*	*Paclitaxel*
Gradishar 2005 Nab-paclitaxel (n=229) vs Paclitaxel (n=225)	23.0 weeks (5.4 mo)	16.9 weeks (4.0mo)	33%	19%	65.0 weeks (15.0 mo)	55.7 weeks (12.9 mo)

Nab-paclitaxel dose 260 mg/m^2 q3w. Paclitaxel dose 175 mg/m^2 q3w.
Nab-paclitaxel: Nanoparticle albumin-bound paclitaxel; PFS: Progression-free survival; TTF: Time to treatment failure; TTP: Time to progression.

Table 6. Phase III trial of nab-paclitaxel monotherapy in mBC – dosage and patient characteristics.

Phase III study	Paclitaxel (nab-paclitaxel)			Patient characteristics: paclitaxel arm (nab-paclitaxel)					
	Dosage	Median no. cycles	Median relative dose intensity	Age in years Mean (median)	ER (+) (%)	HER2 (+) (%)	Number (%) of patients with <3 metastatic sites	Previous adjuvant chemo; number (%)	Previous chemo for metastatic disease; number (%)
Gradishar 2005 Nab-paclitaxel (n=229) vs Paclitaxel (n=225)	175 mg/m^2 q3w (260 mg/m^2 q3w)	NR	NR	53.3 (53.1)	NR	NR	28 (21)	NR	60 (58)

Nab-paclitaxel: Nanoparticle albumin-bound paclitaxel; NR: Not reported; q3w: Every 3 weeks.

Table 7. Phase III trial of gemcitabine-taxane combinations in mBC.

Phase III study	Median PFS/TTP/TTF		Objective response rate (ORR)		Median overall survival (OS)	
	GemPac	*Paclitaxel*	*GemPac*	*Paclitaxel*	*GemPac*	*Paclitaxel*
Albain 2008 GemPac (n=266)[a] vs Paclitaxel (n=263)	6.14 months	3.98 months	41.4%	26.2%	18.6 months	15.8 months
	GD	*CD*	*GD*	*CD*	*GD*	*CD*
Chan 2009 GD[b] (n=153) vs CD[c] (n=152)	8.05 months	7.98 months	32%	32%	19.29 months	21.45 months

CD: Capecitabine + docetaxel; GD: Gemcitabine + docetaxel; GemPac: Gemcitabine + paclitaxel; PFS: Progression-free survival; TTF: Time to treatment failure; TTP: Time to progression. [a]Gemcitabine 1250 mg/m^2 d1, d8, q3w. [b]Gemcitabine 1000 mg/m^2 d1, d8, q3w. [c]Capecitabine 1250 mg/m^2 bd d1-14, q3w

Table 8. Phase III trials of gemcitabine-taxane combinations in mBC – dosage and patient characteristics.

Phase III study	Taxane			Patient characteristics					
	Dosage	Median no. cycles	Median relative dose intensity	Age in years Mean (median)	ER (+) (%)	HER2 (+) (%)	Number (%) of patients with <3 metastatic sites	Previous adjuvant chemo; number (%)	Previous chemo for metastatic disease; number (%)
Albain 2008 GemPac (n=266)[a] vs Paclitaxel (n=263)	175 mg/m^2 q3w*	*Mean* GemPac 6.4; Pac 5.7	GemPac 92.8%; Pac 96.2%	GemPac 53; Pac 53	GemPac 33.1; Pac 31.9	NR	GemPac 56.8; Pac 58.6	GemPac 266 (100); Pac 261 (99.2)	0 (0)
Chan 2009 GD[b] (n=153) vs CD[c] (n=152)	75 mg/m^2 q3w*	*Median* GD 6 CD 6	GD 0.888 CD 0.888	GD 56; CD 53	NR	GD 18 CD 16	GD 52 CD 54	GD 63 CD 66	GD 24 GD 20

CD: Capecitabine + docetaxel; GD: Gemcitabine + docetaxel; GemPac: Gemcitabine + paclitaxel; Pac: Paclitaxel; [a]Gemcitabine 1250 mg/m^2 d1, d8, q3w. [b]Gemcitabine 1000 mg/m^2 d1, d8, q3w. [c]Capecitabine 1250 mg/m^2 bd d1-14, q3w. *Until disease progression or unacceptable toxicity.

Table 9. Phase III trials of paclitaxel versus docetaxel monotherapy.

Phase III study (mBC)	**Median time to progression (TTP)**		**Objective response rate (ORR)**		**Median overall survival (OS)**	
Jones 2005 Docetaxel (n=225) vs paclitaxel (n=224)	*Docetaxel q3w*	*Paclitaxel q3w*	*Docetaxel q3w*	*Paclitaxel q3w*	*Docetaxel q3w*	*Paclitaxel q3w*
	5.7 months	3.6 months	32.0%	25.0%	15.4 months	12.7 months

Phase III study (EBC)	**5-year disease-free survival rate**				**5-year overall survival (OS) rate**			
Sparano 2008 Paclitaxel q3w (n=1253) vs paclitaxel qw (n=1231) vs docetaxel q3w (n=1236) vs docetaxel qw (n=1230)	*Docetaxel q3w*	*Docetaxel qw*	*Paclitaxel q3w*	*Paclitaxel qw*	*Docetaxel q3w*	*Docetaxel qw*	*Paclitaxel q3w*	*Paclitaxel qw*
	81.2%	77.6%	76.9%	81.5%	87.3%	86.2%	86.5%	89.7%
HR vs paclitaxel q3w (95% CI)	1.23 (1.00-1.52) p=0.02	1.09 (0.89-1.34) p=0.29	n/a	1.27 (1.03-1.57) p=0.006	1.13 (0.88-1.46) p=0.25	1.02 (0.80-1.32) p=0.80	n/a	1.32 (1.02-1.72) p=0.01

CI: Confidence interval; EBC: Early breast cancer; HR: Hazard ratio; q3w: Every 3 weeks; qw: Weekly; mBC: Metastatic breast cancer.

Table 10. Phase III trials of paclitaxel versus docetaxel monotherapy – dosage and patient characteristics.

Phase III study (mBC)		Dosage	Median no. cycles	Median relative dose intensity	Age in years Mean (median)	ER (+) (%)	HER2 (+) (%)	Number (%) of patients with <3 metastatic sites	Previous adjuvant chemo; number (%)	Previous chemo for metastatic disease; number (%)
Jones 2005	*Docetaxel q3w (n=225)*	100 mg/m^2 q3w*	6	1.0	56	51.1	NR	median 2, (range 1-5)	51.6	58.2
	Paclitaxel q3w (n=224)	175 mg/m^2 q3w*	4	1.0	54	42.0	NR	median 2, (range 1-6)	53.2	52.7

Phase III study (EBC)		Dosage	Mean no. cycles	Age (median)	ER(+)/ PR(+) (%)	HER2(+) (%)
Sparano 2008†	*Docetaxel q3w (n=1236)*	100 mg/m^2 q3w x 4	3.8	51 years	70.1	18.9
	Docetaxel qw (n=1230)	35 mg/m^2 q3w x 12	10.8	51 years	70.7	18.7
	Paclitaxel q3w (n=1253)	175 mg/m^2 q3w x 4	3.9	51 years	69.2	20.5
	Paclitaxel qw (n=1231)	80 mg/m^2 qw x 12	11.4	51 years	68.2	18.6

* Given until disease progression, unacceptable toxicity or patient withdrawal. †Patients received doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) q3w for 4 cycles. Patients were then randomised to 12 weeks of paclitaxel q3w, paclitaxel qw, docetaxel q3w or docetaxel qw. EBC: Early breast cancer; mBC: Metastatic breast cancer; NR: Not reported; q3w: Every 3 weeks; qw: Weekly.

Gemcitabine plus paclitaxel (GT) (q3w) improved outcomes versus paclitaxel alone in a study of 529 patients (Albain *et al.* 2008). The median TTP increased from 3.98 to 6.14 months, objective response rate increased from 26.2% to 41.4% and median overall survival increased from 15.8 to 18.6 months when gemcitabine was added to paclitaxel. Haematologic toxicity was more commonly observed on GT, especially neutropenia (GT, 47.9% grade 3 or 4; paclitaxel, 11.5%). Febrile neutropenia occurred in 5.0% of patients on GT and 1.2% on paclitaxel. Grade 3 or 4 fatigue was more common on the GT arm; grade 2, 3, or 4 sensory neuropathy occurred at similar frequency (24.1% GT, 21.6% paclitaxel); 8.8% on GT had motor neuropathy, versus 3.1% on paclitaxel.

Another study, in 306 patients showed that the addition of gemcitabine to docetaxel resulted in an increased TTP versus docetaxel alone (7.5 vs 6.5 months) (Nielsen *et al.* 2009). In a study of 305 patients randomised to treatment with gemcitabine plus docetaxel versus capecitabine plus docetaxel, there was no difference in terms of objective response (32% in both arms) and median PFS (8.05 vs 7.98 months, respectively, p=not significant) (Chan *et al.* 2009) (Table 7). NICE has recommended that gemcitabine, in combination with paclitaxel, is an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate (NICE TA116 2007).

Addition of lapatinib to paclitaxel however, in a trial of 579 largely HER2-negative or HER2-unknown patients, showed no improvement versus paclitaxel alone in terms of TTP. There was an improvement in objective response rate (35.1% vs 25.3%) with this combination therapy (Di Leo *et al.* 2008).

Thus, as shown in Table 11, the NICE-recommended combinations of capecitabine or gemcitabine with taxanes in the first-line therapy of metastatic breast cancer, gave a reduction in the risk of progression 30-35%, as shown by the hazard ratio for PFS. The median TTP/PFS was increased to 6.1 months with both combinations, the objective response rate was increased to 41-42% and the median overall survival rose to 14-19 months with these agents in combination with taxanes. However, in common with other

studies of combination chemotherapy, these gains in efficacy came at the expense of increased grade 3-4 toxicities.

Table 11. Indirect comparison of level of benefit reported for addition of non-anthracycline agents to taxane in first-line therapy of metastatic breast cancer.

	Capecitabine + docetaxel (n=255)*	Docetaxel** (n=256)	Gemcitabine+ + paclitaxel† (n=267)	Paclitaxel† (n=262)
Reference	O'Shaughnessy 2002		Albain 2008	
TTP/PFS (mo)	6.1[1]	4.2	6.14[2]	3.98
Hazard Ratio vs monotherapy	0.65		0.70	
Overall Survival (mo)	14.5[1]	11.5	18.6[2]	15.8
Hazard Ratio vs monotherapy	0.77		0.82	
Objective Response (%)	42[1]	30	41.4[2]	26.2

* Capecitabine 1250mg/m^2 bid, d1-14 + docetaxel 75mg/m^2 d1, q21d; ** Docetaxel 100mg/m^2 d1 q21d; + Gemcitabine 1250mg/m^2 d1, 8; †Paclitaxel 175mg/m^2 d1, q21d.

Patients with HER2-positive disease are not included in the scope of the current appraisal. However, for such patients it has been shown that addition of the HER2-targeted monoclonal antibody trastuzumab to taxane chemotherapy very significantly improves efficacy (Slamon *et al.* 2001, Marty *et al.* 2005). Addition of trastuzumab to paclitaxel q3w in HER2-positive patients, increased median time to progression from 3.0 to 6.9 months, objective response rate from 16 to 38% and median overall survival from 18.4 to 22.1 months (Slamon *et al.* 2001). Trastuzumab added to docetaxel q3w in HER2-positive patients increased median time to progression from 6.1 to 11.7 months, objective response rate from 34 to 61% and median overall survival from 22.7 to 31.2 months (Marty *et al.* 2005). These studies demonstrate that addition of a targeted therapy to first-line chemotherapy can, in appropriate patients, provide very significant improvements in efficacy.

The clinical need for improved therapeutic efficacy.

Typically, the chance of an individual patient achieving a durable response decreases by one half with each subsequent chemotherapy regimen. The duration of response also shortens dramatically following second- and third-line chemotherapy, so that each line of therapy confers a decreasing therapeutic benefit (Wood *et al.* 2005, Cardoso *et al.* 2002; Burstein *et al.* 2008). This decrease in benefit, added to the intense patient fear of disease progression (Herschbach *et al.* 2004), creates a compelling drive to seek means of increasing the proportion of patients who respond to first-line therapy and to prolong disease remission in those responders. In particular, those patients who relapse most rapidly after responding to first-line therapy tend also to have a short overall survival, demonstrating their lack of durable responses to subsequent therapies. Such patients, generally labelled as those with 'high-risk' disease, have a very great unmet need for more effective therapies. As shown earlier, this may include patients with triple-negative disease, with Grade 3 tumours, or with positive nodes or large tumours at diagnosis.

Increasing the benefit provided by taxanes in the first-line metastatic setting, by raising the response rate and extending the duration of remission, should significantly improve the therapeutic outcome for patients with high risk disease, who relapse and die rapidly despite the best therapy currently available. Inevitably, combinations of cytotoxic agents show an increase in toxicities such as neutropenia, neuropathy and diarrhoea. A new agent which, in addition to giving a very significant increase in response rate and duration, did not add to the patients' burden of toxic side-effects, should be of considerable value in this setting.

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

4.2.1 Angiogenesis as a target for anticancer therapy

The observation that tumour growth is accompanied by increased vascularity was made more than a century ago (see review by Ferrara 2002). By 1945 it had been suggested that tumour growth was dependent on vascularisation (Algire *et al.* 1945) and that this might be the result of stimulatory factors released from the tumour (Ide *et al.* 1939).

However it was not until 1971 that Folkman proposed that attacking the growth of the new blood vessels which feed the growing tumour (angiogenesis) might be a profitable therapeutic strategy in oncology, which could cause the strangulation of tumours, restrict their regrowth and prevent the growth of new metastatic deposits.

Angiogenesis is a particularly attractive therapeutic target for several reasons:

- The process is relatively unimportant in most adult tissues. The exceptions being areas of damage repair and the lining of the womb during the menstrual cycle. Therefore, it is feasible that interference with angiogenesis might have a relatively limited impact on healthy tissue
- It involves preventing the growth of non-cancerous blood vessel cells, which have greater genetic stability than malignant cells, reducing the chances of the target becoming resistant to any therapeutic intervention as a result of mutation.

In breast cancer, the density of microvessels and other angiogenic markers in histologic specimens correlates with disease recurrence and inversely correlates with survival (Horak *et al.* 1992; Gasparini & Harris 1995; Kato *et al.* 2007; Linderholm *et al.* 2008; Xie *et al.* 2009), underlining the significance of angiogenesis as a component of breast cancer pathogenesis and a possible site of intervention for a therapeutic agent.

4.2.2 VEGF as a pivotal molecule in the control of angiogenesis

In the 1970's and 1980's an intensive search was undertaken for endogenous pro- and anti-angiogenic factors, which might influence new blood vessel formation. One of the most promising of these was vascular endothelial growth factor (VEGF, also known as VEGF-A), a powerful pro-angiogenic glycoprotein produced by both normal and neoplastic cells and first isolated by Ferrara and Henzel in 1989.

Released from tumours, VEGF plays a key role in encouraging nearby blood vessels to sprout and provide a vascular supply to the tumour. Although angiogenesis is a complex process involving the action of multiple ligands and receptors, VEGF-signalling often represents a rate limiting step and hence an effective point of intervention (Ferrara *et al.* 2004). An important role for VEGF in human cancer is indicated by the almost universal

overexpression of this glycoprotein in human cancers examined to date, including those of the breast, lung, thyroid, gut, kidney, bladder, ovary and cervix (Ferrara *et al.* 2004). Inhibition of VEGF therefore appeared to be a prime target for anticancer therapy, with the potential for selective anti-tumour activity at a limited cost in normal tissue toxicity.

Early evidence that interference with VEGF signalling represented a viable approach to cancer therapy came from studies in which a murine anti-VEGF antibody (A.4.6.1; the precursor to bevacizumab) successfully inhibited the growth of a variety of human tumour cell lines grown as xenografts in mice, but not as *in vitro* cell cultures (Kim *et al.* 1993). Further reports indicated that antibody A.4.6.1 could inhibit the growth of a wide range of human tumours, including colorectal cancers, grown in animals (Warren *et al.* 1995; Ferrara *et al.* 2004).

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

Bevacizumab is a 93% human and 7% murine immunoglobulin of the IgG1 subclass, produced by recombinant DNA technology using chinese hamster ovary cells. Bevacizumab binds all isotypes of human VEGF, with an affinity similar to the original murine antibody A.4.6.1 (K_d approximately 0.5 nm), resulting in depletion of the biologically active free molecule. The pharmacokinetics of bevacizumab are linear at doses ranging from 1 to 10mg/kg and the elimination half-life is 18-20 days, allowing for depletion of active VEGF with dosing q3w. When administered systemically, this produces inhibition of angiogenic processes which are reliant upon VEGF signalling.

The blood supply of tumours contains many immature blood vessels, which have not recruited pericyte support cells to surround the endothelial cells that form a complete lining for all the vessels in the body. Withdrawal of VEGF has been shown to lead to the selective apoptosis of endothelial cells in these immature tumour vessels (Benjamin *et al.* 1999). This effect results in the regression of micro-vessels within the tumour (Willet *et al.* 2004; Baluck *et al.* 2005). Inhibition of VEGF signalling also reduces the abnormal permeability of tumour vasculature, thereby reducing interstitial pressure and creating a

more normal blood flow through the tumour (Willet *et al.* 2004; Gerber & Ferrara 2005; Jain 2005). Finally, prolonged inhibition of VEGF signalling inhibits the sprouting and growth of new vessels within and around the tumour (Inai *et al.* 2004, Gerber & Ferrara 2005).

The effects of these changes in tumour vasculature are likely to be two-fold. Initially, the reduction in tumour interstitial pressure and normalisation of tumour vasculature, via inhibition of VEGF signalling, may increase the delivery of cytotoxic therapies to the tumour cells, as has been shown in animal model studies (Wildiers *et al.* 2003; Willet *et al.* 2004). Longer term, prevention of new vessel sprouting and growth within and around the tumour should retard the regrowth and recurrence of primary tumours and prevent the development of new secondary metastatic deposits (Warren *et al.* 1995).

Two recent publications have generated debate on the subject of resistance, regrowth and potential 'rebound' in relation to angiogenesis inhibition (Paez-Ribes *et al.* 2009; Ebos *et al.* 2009). Observations from transgenic mouse models suggested an increase in tumour invasiveness and metastatic spread when tumour-bearing mice, or immuno-suppressed mice transplanted with tumour cell lines, were exposed to antioangiogenic therapy. The angiogenesis inhibitors used in these studies were a VEGF receptor tyrosine kinase inhibitor or a VEGF receptor antibody. This tumour model work did not address VEGF ligand binding, the key mechanism of action of bevacizumab.

An analysis was undertaken of bevacizumab clinical studies which enrolled a total of 4,207 patients with metastatic disease: BO17705 in renal cell cancer, BO17706 in pancreatic cancer, BO17708 (AVADO) in breast cancer, and NO16966 and AVF2107g in colorectal cancer. This analysis found no evidence of accelerated disease progression in the bevacizumab versus the placebo treatment arms, after discontinuation of bevacizumab or placebo due to side effects. Mortality rates at 30, 60 and 90 days were similar in bevacizumab and placebo arms after discontinuation of bevacizumab or placebo (due to any reason or side effects). Moreover, post-progression survival was similar in the patients treated with chemotherapy regimens plus bevacizumab and in

those treated with chemotherapy without bevacizumab (Hurwitz *et al.* 2004; Giantonio *et al.* 2007; Saltz *et al*. 2008; Sandler *et al.* 2006; Manegold *et al*. 2007).

Thus the available clinical evidence suggests that patients treated with bevacizumab in the metastatic setting do not experience more rapid tumour regrowth after the end of their bevacizumab therapy.

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

Although successful in slowing tumour growth and producing measurable tumour shrinkage, pre-clinical studies did not suggest that anti-VEGF therapy alone could produce tumour eradication. This led to the concept of combining anti-angiogenic and conventional cytotoxic agents, an approach which was demonstrated pre-clinically to result in additive antitumour activity (Klement *et al.* 2000).

In breast cancer it is anticipated that bevacizumab will be used in combination with the currently available cytotoxic chemotherapies. The present application concerns the use of bevacizumab in combination with paclitaxel in the first-line treatment of metastatic breast cancer.

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

In the first-line treatment of metastatic breast cancer, therapy is tailored to the individual patient, dependent on age, performance status, prior adjuvant therapies and local practice. Although anthracyclines may be regarded as the gold-standard therapy, their use in the first-line metastatic setting is restricted to patients who have not received prior adjuvant anthracycline therapy. For patients who have already received the maximum permissible anthracycline dose or who are otherwise unsuitable for anthracycline therapy, first-line taxane therapy is regarded as optimal.

The NICE clinical Guideline 81 'Advanced breast cancer: diagnosis and treatment', recommends that:- "For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

- first line: single-agent docetaxel
- second line: single-agent vinorelbine or capecitabine
- third line: single-agent capecitabine or vinorelbine

Qualifying statement: This recommendation was based on the findings of a health economic analysis that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens, for patients who are anthracycline resistant or for whom anthracycline therapy is contraindicated." And "The GDG acknowledged that the existence of price discounts for paclitaxel can significantly alter the cost effectiveness of the sequences examined in the analysis."

Guideline 81 also states that clinicians should "Consider combination therapy for patients for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity" (NICE CG81 2009).

Thus, Guideline 81 recommends first-line taxane therapy for patients unable to take anthracyclines. The Guideline recognises that although docetaxel is in general recommended, in some circumstances paclitaxel might be preferred and that in particular patients, combination therapy may be needed. The Guideline also recognises the importance of the side-effects of therapy to the management of individual patients.

Guideline 81 does not refer to the first-line treatment of metastatic breast cancer patients who have already received adjuvant taxane therapy. The clinician is caught between the need to use the most effective therapy and the prospect that prior taxane therapy may have induced tumour resistance. The treatment of patients whose disease has recurred after adjuvant therapy with an anthracycline and a taxane represents an increasing and unmet clinical need (Conte *et al.* 2007, Biganzoli *et al.* 2008). In current practice,

metastatic patients who received adjuvant taxane therapy are generally only rechallenged with a taxane after an interval of at least 12 months. Even with such a gap between adjuvant and metastatic taxane therapy, it is accepted that patients given prior adjuvant taxane may not respond well to taxane rechallenge and may relapse again after a short interval.

4.6 Provide details of any relevant guidelines or protocols

There are no relevant guidelines or protocols in the UK for the use of bevacizumab in the first-line therapy of metastatic breast cancer.

5 Equity and equality

5.1 Identification of equity and equalities issues

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

The incidence of breast cancer with the worst prognosis varies across racial groups and according to indices of deprivation. This may present issues of access to the most effective therapies for the groups most at risk of early death following a diagnosis of breast cancer.

Of the five common genetic subtypes of breast cancer, the triple-negative (TN) breast cancers, which lack hormone receptors (ER-/PgR-) and are also HER2 negative, have one of the worst outcomes. Women with TN tumours have a worse prognosis than those with other types of breast cancer, with a shorter median time to death, more frequent and earlier distant recurrence and a high early incidence of brain metastases (Dent *et al.* 2007, Dawood *et al.* 2009). For each stage at diagnosis and each ethnic group, patients with TN tumours have a worse survival outlook than patients with other breast tumours (Fulford *et al.* 2007).

In the general breast cancer patient population, 11-13% of breast tumours are TN, but this figure covers considerable heterogeneity of incidence. In particular a high incidence of TN tumours is found in populations of African descent:- in the USA 25-26% of non-Hispanic black patients with breast cancer have TN tumours (Carey *et al.* 2006, Bauer *et al.* 2007). TN disease is also more frequent in both white and black women of the lowest socioeconomic status (Bauer *et al.* 2007) and those living in areas with the greatest poverty index (Vona-Davis *et al.* 2008, Trivers *et al.* 2009). Thus although an elevated incidence of TN breast cancer may be associated with certain racial groups, it is also linked to indicators of deprivation such as low family income.

Because TN breast cancer will not respond to any therapies targeted against specific breast cancer receptors (hormonal or HER2-directed therapies), this group of patients

are poorly served by the currently available therapeutic interventions. The association of a high level of this particularly aggressive form of breast cancer with particular racial groups and with deprived populations therefore presents an issue for the equality of provision of effective breast cancer therapies across the UK population as a whole.

In addition to the elevated incidence of triple-negative breast cancer in women of African descent, there is a general trend for these women to present with breast cancer at a younger age and with more aggressive disease, leading to worse survival compared with their white counterparts (Anderson *et al.* 2005; Carey *et al.* 2006; Baquet *et al.* 2008; Trivers *et al.* 2009). A recent study in East London suggests that the poorer prognosis seen amongst African-American women may also be seen in black British women when compared with white women living in the same area (Bowen *et al.* 2008). Similar to African-American women, Afro-Caribbean women in the UK are more likely to present at a young age, before they are called to the NHS Breast Screening Programme (Bowen *et al.* 2008; Nair *et al.* 2009). Additional UK studies have suggested that women from other ethnic minority groups may also have worse survival outcomes from breast cancer (Jack *et al.* 2009; Cuthbertson *et al.* 2009).

Several large UK studies have also shown that women living in socially deprived areas have a worse prognosis than women living in more affluent areas, with an increased risk of disease recurrence and reduced survival (Kaffashian *et al.* 2003; Mullee *et al.* 2004; Sloggett *et al.* 2007; Shack *et al.* 2007; Downing *et al.* 2007; Rachet *et al.* 2008; Jack *et al.* 2009). Women living in deprived areas in the UK are more likely to present with tumours of a high Grade (Taylor & Cheng 2003; Adams *et al.* 2004), ER-negative tumours (Thomson *et al.* 2001; Taylor & Cheng 2003), large tumours or locally advanced disease (Macleod *et al.* 2000; Henley *et al.* 2005) or disease with lymph node involvement (Adams *et al.* 2004; Downing *et al.* 2007; Wishart *et al.* 2010). All these characteristics are associated with a high risk of rapid relapse after therapy and early death from breast cancer.

There is also a relationship between socioeconomic status and uptake of the NHS Breast Screening Programme in the UK, with women from deprived areas less likely to

attend for mammography (Pfeffer 2004; Maheswaran *et al.* 2006; Werneke *et al.* 2006; Moser *et al.* 2009), reducing their chances of detection early in the course of disease. Women presenting with symptomatic breast cancer have a worse survival prognosis than those with screen-detected cancer (Smith *et al.* 2004; Wishart *et al.* 2008). Symptomatic breast cancers are more likely to be ER-negative, have nodal involvement, a higher histological Grade and larger tumour size, all of which are poor prognositic factors. As a result they are more likely to be treated with adjuvant chemotherapy, including taxanes (Dawson *et al.* 2009).

The lack of availability of the technology under appraisal, bevacizumab, on the NHS means that very few socially-deprived women have access to this therapy. If, as will be shown in this submission, bevacizumab provides particular benefit for patients with poor prognosis disease, the lack of access for socially-deprived women presents an issue for the equality of access to medicines.

How has the analysis addressed these issues?

Patients with triple-negative breast cancer and with high-risk disease have been included in the study presented in this submission. The therapeutic outcomes for the ER-negative and triple-negative patients included in the E2100 study have been described in sub-group analyses and are presented in the relevant sections below. Many of the patients with high-risk disease included in E2100 will have received prior adjuvant taxane therapy. Therapeutic outcomes for the subgroup of patients given prior adjuvant taxane therapy are also presented in the relevant sections below.

6 Clinical evidence

6.1 Identification of studies

The following databases were used to identify relevant studies:

- Medline via Dialog DataStar. Medline 1993 to date (MEYY) and Medline-In process-Latest eight weeks (MEIP) were searched on 18 September 2009. Medline was searched from 1993 to the present, and also the eight weeks prior to 18 September 2009. The searches were updated on 1 February 2010 to capture any records published between preparation of the draft submission and finalising the submission. The upated searches were conducted by repeating the original search strategies with restricted dates - MEYY was searched with dates restricted to 19 September 2009 to the present, MEIP was searched for the eight weeks prior to 1 February 2010.

- Embase via Dialog DataStar. Embase 1993 to date (EMYY) and Embase latest eight weeks (EMBA) were searched on 18 September 2009. Embase was searched from 1993 to the present, and also the eight weeks prior to 18 September 2009. The searches were updated on 1 February 2010 - EMYY was searched with dates restricted to 19 September 2009 to the present, EMBA was searched for the eight weeks prior to 1 February 2010.

- Biosis Previews via Dialog DataStar. Biosis Previews 1993 to date (BIYY) was searched on 18 September 2009. The search was updated on 1 February 2010 - BIYY was searched with dates restricted to 19 September 2009 to the present.

- The Cochrane Library was accessed via Wiley Interscience online at http://www.mrw.interscience.wiley.com/cochrane/cochrane_search_fs.html and searched with unrestricted dates up to 18 September 2009. The search was repeated on 1 February 2010 with unrestricted dates and new records not identified in the original search manually extracted and combined with the original search.

- American Society of Clinical Oncology (ASCO) abstracts for meetings 2004-2009 were searched on 22 September 2009 via the *Journal of Clinical Oncology* archive, with full online access at http://jco.ascopubs.org/search.dtl.

- San Antonio Breast Cancer Symposium (SABCS) abstracts for meetings 2006-2008 were searched on 22 September 2009 online at http://www.sabcs.org/EnduringMaterials/Index.asp#abstracts. Abstracts for the 2009 meeting, which occurred after the original search, were searched online on 2 February 2010 and combined with the results of the original search of the 2006-2008 meetings.

- European CanCer Organisation (ECCO) and European Society for Medical Oncology (ESMO) abstracts for meetings 2007-2009 were searched on 22 September 2009, online:

  ECCO/ESMO 2009, http://ex2.excerptamedica.com/CIW-09ecco/
  ECCO 2007, http://www.posters2view.com/ecco14/welcome.php;
  and in print:
  ESMO 2008, *Annals of Oncology* 2008; 19 (Suppl 8): viii2-viii321
  ESMO 2007, *Annals of Oncology* 2007; 18 (Suppl 9): ix1-ix207

Searches used index and text words which included *bevacizumab* and *breast cancer* as major descriptors. The search was restricted to include only documents relating to humans and clinical trials, and excluded reviews wherever possible. Where possible the search was restricted to metastatic or advanced breast cancer. The search was further restricted manually according to inclusion/exclusion criteria in 6.2.2. There were no restrictions by language.

An overview of the search strategies are presented below. Full details of the searches conducted and terms used are provided in appendix 2, section 10.2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are also provided in appendix 2, section 10.2.

Search strategy for BIOSIS Previews covering search period 1993 – 18 September 2009

No.	Database	Search term	Info added since	Results
1	BIYY	bevacizumab	unrestricted	1824
2	BIYY	BREAST-NEOPLASMS.DS. OR BREAST-CANCER.DS.	unrestricted	79136
3	BIYY	metastatic	unrestricted	56124
4	BIYY	NEOPLASM-METASTASIS.DS.	unrestricted	17174
5	BIYY	3 OR 4	unrestricted	63187
6	BIYY	1 AND 2 AND 5 AND HUMANS#	unrestricted	100
7	BIYY	PT=LITERATURE-REVIEW	unrestricted	414995
8	BIYY	6 NOT 7	unrestricted	82

Search strategy for BIOSIS Previews covering search period 19 September 2009 – 1 February 2010

No.	Database	Search term	Info added since	Results
1	BIYY	BEVACIZUMAB	20090919	276
2	BIYY	BREAST-NEOPLASMS.DS. OR BREAST-CANCER.DS.	20090919	3067
3	BIYY	METASTATIC	20090919	1899
4	BIYY	NEOPLASM-METASTASIS.DS.	20090919	840
5	BIYY	3 OR 4	various	2230
6	BIYY	1 AND 2 AND 5 AND HUMANS#	various	10
7	BIYY	PT=LITERATURE-REVIEW	unrestricted	431783
8	BIYY	6 NOT 7	various	5

Search strategy for EMBASE and MEDLINE covering search period 1993 – 18 September 2009

No.	Database	Search term	Info added since	Results
1	EMYY	bevacizumab.MJ.	unrestricted	1819
2	EMYY	(breast ADJ cancer).MJ.	unrestricted	65745
3	EMYY	metastatic	unrestricted	68336
4	EMYY	METASTASIS.W..DE. OR ADVANCED-CANCER.DE.	unrestricted	81066
5	EMYY	3 OR 4	unrestricted	122060
6	EMYY	1 AND 2 AND 5 AND CLINICAL-TRIAL# AND HUMAN=YES	unrestricted	52
7	EMYY	REVIEW=YES	unrestricted	823799
8	EMYY	6 NOT 7	unrestricted	38
9	MEYY	bevacizumab	unrestricted	3100
10	MEYY	ANTIBODIES-MONOCLONAL.DE.	unrestricted	86209
11	MEYY	9 AND 10	unrestricted	2177
12	MEYY	breast ADJ cancer	unrestricted	96289
13	MEYY	BREAST-NEOPLASMS.MJ.	unrestricted	91986
14	MEYY	12 OR 13	unrestricted	120102
15	MEYY	metastatic	unrestricted	75840
16	MEYY	NEOPLASM-METASTASIS.DE.	unrestricted	26612
17	MEYY	15 OR 16	unrestricted	89551
18	MEYY	advanced ADJ cancer	unrestricted	4352
19	MEYY	17 OR 18	unrestricted	93379
20	MEYY	11 AND 14 AND 19 AND PT=CLINICAL-TRIAL# AND HUMAN=YES	unrestricted	10
21	EMYY MEYY	combined sets 8, 20	unrestricted	48
22	EMYY MEYY	dropped duplicates from 21	unrestricted	10
23	EMYY MEYY	unique records from 21	unrestricted	38

Search strategy for EMBASE and MEDLINE covering search period 18 September 2009 – 1 February 2010

No.	Database	Search term	Info added since	Results
1	EMYY	BEVACIZUMAB.MJ.	20090919	239
2	EMYY	(BREAST ADJ CANCER).MJ.	20090919	2425
3	EMYY	metastatic	unrestricted	71015
4	EMYY	METASTASIS.W..DE. OR ADVANCED-CANCER.DE.	unrestricted	84668
5	EMYY	3 OR 4	various	5174
6	EMYY	1 AND 2 AND 5 AND CLINICAL-TRIAL# AND HUMAN=YES	various	4
7	EMYY	REVIEW=YES	20090919	31076
8	EMYY	6 NOT 7	various	2
9	MEYY	BEVACIZUMAB	20090919	720
10	MEYY	ANTIBODIES-MONOCLONAL.MJ.	20090919	938
11	MEYY	9 AND 10	various	109
12	MEYY	breast ADJ cancer	20090919	7671
13	MEYY	BREAST-NEOPLASMS.MJ.	20090919	2069
14	MEYY	12 OR 13	20090919	8124
15	MEYY	metastatic	20090919	5461
16	MEYY	NEOPLASM-METASTASIS.MJ.	20090919	142
17	MEYY	15 OR 16	20090919	5530
18	MEYY	advanced ADJ cancer	20090919	311
19	MEYY	17 OR 18	20090919	5815
20	MEYY	11 AND 14 AND 19 AND (CLINICAL-TRIALS# OR PT=CLINICAL-TRIAL#) AND HUMAN=YES	various	2
21	EMYY MEYY	combined sets 8, 20	various	4
22	EMYY MEYY	dropped duplicates from 21	various	0
23	EMYY MEYY	unique records from 21	various	4

Search strategy for EMBASE last eight weeks and MEDLINE in process – search conducted on 18 September 2009

No.	Database	Search term	Info added since	Results
1	EMBA	bevacizumab	unrestricted	239
2	EMBA	breast ADJ cancer	unrestricted	1814
3	EMBA	1 AND 2	unrestricted	23
4	EMBA	PT=REVIEW	unrestricted	15669
5	EMBA	3 NOT 4	unrestricted	9
6	MEIP	bevacizumab	unrestricted	267
7	MEIP	breast ADJ cancer	unrestricted	2986
8	MEIP	6 AND 7	unrestricted	23
9	EMBA MEIP	combined sets 5, 8	unrestricted	32
10	EMBA MEIP	dropped duplicates from 9	unrestricted	4
11	EMBA MEIP	unique records from 9	unrestricted	28

Search strategy for EMBASE last eight weeks and MEDLINE in process – search conducted on 1 February 2010

No.	Database	Search term	Info added since	Results
1	EMBA	BEVACIZUMAB	unrestricted	164
2	EMBA	BREAST ADJ CANCER	unrestricted	1552
3	EMBA	1 AND 2	unrestricted	23
4	EMBA	PT=REVIEW	unrestricted	12419
5	EMBA	3 NOT 4	unrestricted	13
6	MEIP	BEVACIZUMAB	unrestricted	437
7	MEIP	breast ADJ cancer	unrestricted	4740
8	MEIP	6 AND 7	unrestricted	32
9	EMBA MEIP	combined sets 5, 8	unrestricted	45
10	EMBA MEIP	dropped duplicates from 9	unrestricted	3
11	EMBA MEIP	unique records from 9	unrestricted	42

Search strategy for Cochrane library – search conducted 18 September 2009 and repeated on 1 February 2010

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 covering search period January 2004 – 22 September 2009

The *Journal of Clinical Oncology* archive was searched for ASCO annual meetings 2004-2009. ASCO Meeting Abstracts was specified as the source to search. No date restrictions were applied. The search was conducted using the terms *bevacizumab* in the Title and *metastatic breast cancer* in the Title or Abstract; or *bevacizumab* in the Title and *advanced breast cancer* in the Title or Abstract. Records from both searched were manually combined.

Search strategy for SABCS abstracts covering search period January 2006 – 2 February 2010

SABCS abstracts were searched online. Abstracts were available online from 2006 to the present. The search was conducted using the terms *bevacizumab* in All fields AND *metastatic breast cancer* in All fields. The search was repeated for each year and the results manually combined.

Search strategy for ECCO/ESMO abstracts covering search period 2007 – September 22 2009

ECCO and ESMO abstracts were searched online and in the *Annals of Oncology* archive. Abstracts were searched using the terms "*bevacizumab metastatic breast cancer*" or "*bevacizumab breast cancer*" or "*bevacizumab*". Records from the online and *Annals of Oncology* archive searches were manually combined.

Table 12 gives the number of records obtained from each of the above sources during searching, and the number of records retained or excluded based on the criteria outlined in section 6.2.2. Details of the search outputs/records obtained and reasons for exclusion/inclusion of records are provided in appendix 2, section 10.2.

Table 12. Records from literature searches identified, excluded and retained.

Source	Records found	Records excluded	Relevant RCT and non-RCT records retained
BIOSIS Previews	87	79	8
EMBASE/ MEDLINE 1993-Present	42	41	1
EMBASE last 8 weeks/ MEDLINE in process (18 September 2009)	28	27	1
EMBASE last 8 weeks/ MEDLINE in process (1 February 2010)	42	42	0
Cochrane library	16	15	1
ASCO abstracts	63	60	3
SABCS abstracts	50	47	3
ECCO/ESMO abstracts	22	21	1
		TOTAL	**18** (11 RCT + 7 relevant non-RCT records)

6.2 Study selection

6.2.1 Complete list of RCTs

Study E2100

1. Gray R et al. Independent review of E2100: A phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol 2009; 27(30): 4966-72.

2. Cameron D et al. Bevacizumab in the first-line treatment of metastatic breast cancer. Eur J Cancer Suppl 2008; 6: 21-28.

3. Klencke B et al. Independent review of E2100 validates progression-free survival (PFS) improvement with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC). J Clin Oncol 2008; 26(May 20 Suppl): 50s, Abstract 1036.

4. Miller K et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New Engl J Med 2007; 357(26): 2666-76.

5. Wagner L et al. Health-related quality of life among patients with metastatic breast cancer receiving paclitaxel versus paclitaxel plus bevacizumab: results from the eastern cooperative oncology group (ECOG) study E2100. Breast Cancer Res Treat 2006; S239, Abstract 5078.

6. Zon R et al. A randomized phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100. Eur J Cancer Suppl 2006; 4(2): 46, Abstract 7.

7. Miller K et al. First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: A randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100). Eur J Cancer Suppl 2005; 3: 77, Abstract 275.

8. Miller K et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005; 94(Suppl 1): S6, Abstract 3.

9. Miller K et al. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003; 3: 421-22.

Study BO17708, AVADO

10. Greil R et al. Quality of life (QoL) in patients (pts) treated with bevacizumab (BV) and taxane therapy for locally recurrent (LR) or metastatic breast cancer (mBC). Eur J Cancer Suppl 2009; 7(2): 266.

11. Pivot X et al. Clinical benefit of bevacizumab (BV) + first-line docetaxel (D) in elderly patients (pts) with locally-recurrent or metastatic breast cancer (mBC): AVADO study. J Clin Oncol 2009; 27: 15s(suppl), Abstract 1094.

12. Dirix L et al. Safety of bevacizumab (BV) plus docetaxel (D) in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) who developed brain metastases during the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)292s, Abstract 4116.

13. Wardley A et al. Effect of anticoagulation therapy on bleeding and thromboembolic events (TEs) in the AVADO phase III study of bevacizumab (BV) plus docetaxel (D) in locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009; 69(Suppl): (2)114s, Abstract 1035.

14. Cortes J et al. Safety of surgery in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) treated with docetaxel (D) plus bevacizumab (BV) or placebo (PL) in the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)113s, Abstract 1030.

15. Chan A et al. Efficacy of bevacizumab (BV) plus docetaxel (D) does not correlate with hypertension (HTN), or G-CSF use in patients (pts) with locally recurrent

(LR) or metastatic breast cancer (mBC) in the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)112s, Abstract 1027.

16. Fumoleau P et al. Maintenance therapy of bevacizumab (BV) results in superior PFS compared with placebo (PL) in the AVADO trial (BV + docetaxel [D] vs D + PL in first-line HER2-negative locally recurrent [LR] or metastatic breast cancer [mBC]). Cancer Res 2009; 69(Suppl) (2)102s, Abstract 903.

17. Miles D et al. Randomised, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol 2008; 26(May 20 Suppl): 43s, Abstract LBA1011 and Oral Presentation.

18. Harbeck N et al. No clinical evidence for increase in tumour aggressiveness or metastatic spread in patients with metastatic breast cancer (mBC) treated with bevacizumab (BV) and docetaxel (D) in the phase III AVADO study. Cancer Res 2009; 69: 852s, Abstract 6086.

19. Miles D et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009; 69: 495s, Abstract 41.

E2100, AVADO and RIBBON-1

20. O'Shaughnessy J et al. 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 Res 2009; 69: 512s, Abstract 207.

21. Robert N et al. Phase III studies of bevacizumab (B) in combination with chemotherapy in patients with HER2-negative metastatic breast cancer (MBC): summary of selected adverse events. Cancer Res 2009; 69: 850-1s, Abstract 6083.

RIBBON-1

22. 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): 264.

23. 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.

24. 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.

Study AVF2119g

25. Miller KD et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23(4): 792-99.

RIBBON-2

26. Brufsky A et al. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. Cancer Res 2009; 69: 495-6s, Abstract 42.

Other studies

27. Mayer E et al. SABRE-B: a randomized phase II trial evaluating the safety and efficacy of combining sunitinib (S) with paclitaxel (P) plus bevacizumab (B) as first-line treatment for HER2-negative metastatic breast cancer (MBC): final results. Cancer Res 2009; 69(2), Suppl: 239S-240S.

28. 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. Eur J Cancer Suppl 2009; 7(2): 277.

29. Lyons JA. Toxicity results and early outcome data on a randomized phase II study of docetaxel +/- bevacizumab for locally advanced, unresectable breast cancer. J Clin Oncol 2006; 24(June 20 Suppl.):133s, Abstract 3049.

Randomised, phase II study of paclitaxel and bevacizumab +/-gemcitabine as first-line treatment for metastatic breast cancer

30. Hoelzer K et al. Preliminary results of a randomized phase II study of paclitaxel and bevacizumab ± gemcitabine as first-line treatment for metastatic breast cancer. J Clin Oncol 2009; 27: 15s, Abstract 1089.

31. Brufsky A et al. A phase II study of paclitaxel and bevacizumab +/-gemcitabine as first-line treatment for metastatic breast cancer (MBC): Interim safety results. J Clin Oncol 2008; 26(May 20 Suppl.): 64s, Abstract 1095.

6.2.2 Inclusion and exclusion criteria

Inclusion criteria

Published papers or abstracts which evaluated the following were included:

1. 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
2. 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
3. Studies in which patients received bevacizumab therapy in combination with paclitaxel or docetaxel, to be consistent with the bevacizumab licence. Data addressing the efficacy of bevacizumab in combination with other agents are not in line with the licence
4. 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 second or later lines of treatment are not in line with the licence

5. Patient population had to consist predominantly of HER2-negative patients (≥90%), as this is the patient population of interest for this appraisal
6. 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
7. Safety data from studies in which bevacizumab was used in humans with metastatic breast cancer in combination with paclitaxel or docetaxel
8. Clinical trial data – rather than case reports, retrospective reviews, etc.
9. Controlled studies
10. Documents relating to humans – since work in animal models is not relevant to this application

Exclusion criteria

Published papers or abstracts which evaluated the following were excluded:

1. Any references providing a review or commentary on data previously published elsewhere were excluded, as only current clinical trial data are required
2. Any papers where duplicate records were already identified through other searches
3. Studies in which bevacizumab was administered in combination with chemotherapeutic agents other than paclitaxel or docetaxel (as per licence) and/or 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
4. Studies in which the partner agent was not given according to routine UK clinical practice
5. Studies in which the comparator was an unlicensed agent, or bevacizumab was used in combination with an unlicensed agent
6. Studies in which the difference between treatment arms was the addition of an agent other than bevacizumab (e.g., paclitaxel + bevacizumab vs paclitaxel + bevacizumab + agent A), and which therefore do not provide any data on the effects on efficacy and safety of adding bevacizumab to a relevant agent

7. Studies not powered to detect a difference between the efficacy and/or safety of bevacizumab in combination with a relevant partner agent (i.e., paclitaxel or docetaxel) and a comparator
8. Patient population n<100
9. References from ongoing studies providing insufficient data – e.g., patient demographics/study design described but no efficacy data available
10. Animal studies or *in vitro* research – only human data are required

Additional inclusion criteria

Non-randomised controlled trials were also considered for relevance to the decision problem, as outlined in section 6.2.4. Non-RCTs were considered according to the following inclusion criteria:

1. Relevant patient population (i.e., first-line metastatic breast cancer, ≥90% HER2-negative)
2. Partner agent/s in line with the bevacizumab licence (paclitaxel and/or docetaxel)
3. Large study population (n>1000)
4. Safety data available from a large number of patients receiving bevacizumab in combination with either paclitaxel or docetaxel

6.2.3 List of relevant RCTs

Please refer to Figure 1 at the end of section 6.2 for a flow diagram of the numbers of studies included and excluded at each stage.

Relevant RCTs

Study E2100

This was an open-label, active controlled, phase III study in which 722 patients were randomised to receive treatment with either bevacizumab (10 mg/kg every 2 weeks [q2w]) plus paclitaxel (90 mg/m^2 weekly for 3 weeks followed by a 1 week rest) or paclitaxel monotherapy.

1. Gray R et al. Independent review of E2100: A phase III trial of bevacizumab plus paclitaxel versus paclitaxel in women with metastatic breast cancer. J Clin Oncol 2009; 27(30): 4966-72.

2. Cameron D et al. Bevacizumab in the first-line treatment of metastatic breast cancer. Eur J Cancer Suppl 2008; 6: 21-28.

3. Klencke B et al. Independent review of E2100 validates progression-free survival (PFS) improvement with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC). J Clin Oncol 2008; 26(May 20 Suppl): 50s, Abstract 1036.

4. Miller K et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New Engl J Med 2007; 357(26): 2666-76.

5. Wagner L et al. Health-related quality of life among patients with metastatic breast cancer receiving paclitaxel versus paclitaxel plus bevacizumab: results from the eastern cooperative oncology group (ECOG) study E2100. Breast Cancer Res Treat 2006; S239, Abstract 5078.

6. Zon R et al. A randomized phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100. Eur J Cancer Suppl 2006; 4(2): 46, Abstract 7.

7. Miller K et al. First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: A randomized, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100). Eur J Cancer Suppl 2005; 3: 77, Abstract 275.

8. Miller K et al. A randomized phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005; 94(Suppl 1): S6, Abstract 3.

9. Miller K et al. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003; 3: 421-22.

E2100, AVADO and RIBBON-1

The following two references each present summaries of data from three phase III RCTs including E2100.

10. O'Shaughnessy J et al. 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 Res 2009; 69: 512s, Abstract 207.

11. Robert N et al. Phase III studies of bevacizumab (B) in combination with chemotherapy in patients with HER2-negative metastatic breast cancer (MBC): summary of selected adverse events. Cancer Res 2009; 69: 850-1s, Abstract 6083.

Excluded RCTs

Records for the RCTs listed below were obtained in full for further investigation. These records were excluded based on exclusion criteria listed in section 6.2.2. A brief discussion of the rationale for excluding each study is provided below the relevant reference citations.

Study BO17708, AVADO

1. Greil R et al. Quality of life (QoL) in patients (pts) treated with bevacizumab (BV) and taxane therapy for locally recurrent (LR) or metastatic breast cancer (mBC). Eur J Cancer Suppl 2009; 7(2): 266.

2. Pivot X et al. Clinical benefit of bevacizumab (BV) + first-line docetaxel (D) in elderly patients (pts) with locally-recurrent or metastatic breast cancer (mBC): AVADO study. J Clin Oncol 2009; 27: 15s(suppl), Abstract 1094.

3. Dirix L et al. Safety of bevacizumab (BV) plus docetaxel (D) in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) who developed brain metastases during the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)292s, Abstract 4116.

4. Wardley A et al. Effect of anticoagulation therapy on bleeding and thromboembolic events (TEs) in the AVADO phase III study of bevacizumab (BV) plus docetaxel (D) in locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009; 69(Suppl): (2)114s, Abstract 1035.

5. Cortes J et al. Safety of surgery in patients (pts) with locally recurrent (LR) or metastatic breast cancer (mBC) treated with docetaxel (D) plus bevacizumab (BV) or placebo (PL) in the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)113s, Abstract 1030.

6. Chan A et al. Efficacy of bevacizumab (BV) plus docetaxel (D) does not correlate with hypertension (HTN), or G-CSF use in patients (pts) with locally recurrent

(LR) or metastatic breast cancer (mBC) in the AVADO phase III study. Cancer Res 2009; 69(Suppl): (2)112s, Abstract 1027.

7. Fumoleau P et al. Maintenance therapy of bevacizumab (BV) results in superior PFS compared with placebo (PL) in the AVADO trial (BV + docetaxel [D] vs D + PL in first-line HER2-negative locally recurrent [LR] or metastatic breast cancer [mBC]). Cancer Res 2009; 69(Suppl) (2)102s, Abstract 903.

8. Miles D et al. Randomised, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol 2008; 26(May 20 Suppl): 43s, Abstract LBA1011 and Oral Presentation.

9. Harbeck N et al. No clinical evidence for increase in tumour aggressiveness or metastatic spread in patients with metastatic breast cancer (mBC) treated with bevacizumab (BV) and docetaxel (D) in the phase III AVADO study. Cancer Res 2009; 69: 852s, Abstract 6086.

10. Miles D et al. Final overall survival (OS) results from the randomised, double-blind, placebo-controlled, phase III AVADO study of bevacizumab (BV) plus docetaxel (D) compared with placebo (PL) plus D for the first-line treatment of locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009; 69: 495s, Abstract 41.

AVADO was a randomised, double-blind, placebo-controlled, multicentre, Phase III study of 736 patients evaluating the efficacy and safety of bevacizumab in combination with docetaxel in comparison with docetaxel plus placebo, as first-line treatment for HER2-negative locally advanced or metastatic breast cancer. The primary objective of this study was to compare progression-free survival in patients randomised to bevacizumab 7.5 mg/kg and docetaxel every 3 weeks (q3w), or bevacizumab 15 mg/kg and docetaxel q3w, versus placebo and docetaxel q3w.

In the AVADO study, all patients were given docetaxel at a dose of 100 mg/m^2 q3w for up to nine cycles. This dosing regimen is not representative of routine NHS clinical

practice, where clinicians generally treat first-line metastatic breast cancer patients with docetaxel 75mg/m^2 q3w for a maximum of 6, or in exceptional cases 8, cycles (protocols in many tertiary centres, including Royal Marsden Hospital). Hospital sales data from IMS show that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles q3w, at an average planned dose of 150mg (or 79mg/m^2 for an average 1.9m^2 patient).

A docetaxel dose of 100mg/m^2 is associated with a significant burden of adverse events, giving a tolerability profile which UK clinicians do not regarded as appropriate in the palliative treatment of most first-line metastatic breast cancers. Because the dosing of docetaxel in this study is not reflective of routine NHS clinical practice (exclusion criterion 4) and also because bevacizumab in combination with docetaxel would be far from cost-effective for the NHS, the AVADO study is not considered relevant to this submission.

RIBBON-1

11. 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): 264.

12. 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.

13. 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.

RIBBON-1 was a randomised, placebo-controlled, Phase III study of 1237 patients investigating bevacizumab in combination with either taxane-based, anthracycline-based or capecitabine chemotherapies in the first-line treatment of HER2-negative locally recurrent or metastatic breast cancer. Patients were entered into one of two cohorts, capecitabine (n=615) or taxane/anthracycline (n=622), and then randomised to receive the chosen chemotherapy with either bevacizumab or placebo (2:1 ratio). Within the taxane/anthracycline cohort, some patients received docetaxel with bevacizumab (n=122) or placebo (n=58).

The complete taxane/anthracycline cohort had 90% power to detect a HR of 0.7 for PFS, based on a sample size of 600 patients. The study was not powered to provide any individual endpoints for the 180 patients treated with bevacizumab plus docetaxel versus placebo plus docetaxel. Therefore, due to the small number of patients receiving bevacizumab with a relevant partner agent (docetaxel) in this trial, and the fact that the study was not powered to provide endpoints for bevacizumab plus docetaxel, this study has been excluded (in accordance with exclusion criterion 7).

Study AVF2119g

14. Miller KD et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23(4): 792-99.

This study investigated bevacizumab plus capecitabine versus capecitabine alone in 462 patients with metastatic breast cancer. Patients who had received prior chemotherapy for metastatic disease were eligible for inclusion. The study population consisted of 16% of patients who had received no prior chemotherapy for metastatic disease, 44% who had received one line of chemotherapy for metastatic disease and 40% who had received two or more. Therefore, the study population is not considered relevant because few (16%) of the patients were first-line metastatic breast cancer patients, which is the patient population of interest for this appraisal. In addition, the partner agent to bevacizumab in this trial was capecitabine, which is not licensed for use in

combination with bevacizumab and is not one of the agents being considered in this appraisal. This trial has been excluded in accordance with exclusion criterion 3.

RIBBON-2

15. Brufsky A et al. RIBBON-2: A randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of HER2-negative metastatic breast cancer. Cancer Res 2009; 69: 495-6s, Abstract 42.

This ongoing randomised, placebo-controlled study is investigating bevacizumab in combination with a taxane or other chemotherapy in the second-line treatment of metastatic breast cancer. All patients have received one prior line of cytotoxic therapy for metastatic disease. This trial has been excluded in accordance with exclusion criterion 3.

Other studies

16. Mayer E et al. SABRE-B: a randomized phase II trial evaluating the safety and efficacy of combining sunitinib (S) with paclitaxel (P) plus bevacizumab (B) as first-line treatment for HER2-negative metastatic breast cancer (MBC): final results. Cancer Res 2009; 69(2), Suppl: 239S-240S.

The SABRE-B trial investigated the addition of sunitinib to bevacizumab plus paclitaxel in the first-line treatment of 46 patients with metastatic breast cancer. The difference between treatment arms was the addition of sunitinib. Therefore, this was a trial of sunitinib, not bevacizumab, and does not provide any data on the effects on efficacy and safety of adding bevacizumab to a relevant agent. This trial has been excluded in accordance with exclusion criteria 6 and 8.

17. 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. Eur J Cancer Suppl 2009; 7(2): 277.

This is a preliminary report from an ongoing study. At the time of reporting, 84 patients of a planned 490 had been enrolled onto the study. The report provides baseline characteristics of the patients enrolled to date, but no efficacy data, and therefore does not provide any information relevant to the decision problem. This study was excluded in accordance with exclusion criterion 9.

18. Lyons JA. Toxicity results and early outcome data on a randomized phase II study of docetaxel +/- bevacizumab for locally advanced, unresectable breast cancer. J Clin Oncol 2006; 24(June 20 Suppl.):133s, Abstract 3049

This study investigated the addition of bevacizumab to docetaxel as part of a neoadjuvant regimen in 49 patients with locally advanced breast cancer; therefore, the treatment setting (neoadjuvant) was not relevant to the decision problem (metastatic). This study was excluded as the treatment in accordance with exclusion criteria 3 and 8.

Randomised, phase II study of paclitaxel and bevacizumab +/-gemcitabine as first-line treatment for metastatic breast cancer

19. Hoelzer K et al. Preliminary results of a randomized phase II study of paclitaxel and bevacizumab ± gemcitabine as first-line treatment for metastatic breast cancer. J Clin Oncol 2009; 27: 15s, Abstract 1089.

20. Brufsky A et al. A phase II study of paclitaxel and bevacizumab +/-gemcitabine as first-line treatment for metastatic breast cancer (MBC): Interim safety results. J Clin Oncol 2008; 26(May 20 Suppl.): 64s, Abstract 1095.

This ongoing study is investigating the addition of gemcitabine to bevacizumab plus paclitaxel in the first-line treatment of metastatic breast cancer. The difference between treatment arms is the addition of gemcitabine. Therefore, this is a trial of gemcitabine,

not bevacizumab, and does not provide any data on the effects on efficacy and safety of adding bevacizumab to a relevant agent. The most recent report (Hoelzer *et al.* 2009) provides data on 61 patients randomised to bevacizumab/paclitaxel and 58 randomised to bevacizumab/paclitaxel plus gemcitabine. This trial has been excluded in accordance with exclusion criteria 6 and 8.

6.2.4 List of relevant non-randomised controlled trials

Study MO19391, ATHENA

This was a large (n=2,251), open-label study of bevacizumab plus a taxane (monotherapy or in combination) or non-anthracycline chemotherapy for the first-line treatment of patients with HER2-negative locally recurrent or metastatic breast cancer. The primary objective of this study was to assess the safety profile of bevacizumab 10 mg/kg q2w or 15 mg/kg q3w in combination with taxane therapy in the first-line treatment of patients with locally recurrent/metastic breast cancer.

ATHENA has reported primary and updated analyses. The study has been included because it has a very large safety population, allowing for detection of rare adverse events and providing a large body of safety data. The patient entry criteria are also more similar to 'routine clinical practice' than the Phase III RCTs. Most patients (78%) received taxane-based therapy with bevacizumab, predominantly paclitaxel or docetaxel monotherapy.

1. Cortes-Funes H et al. Multinational study (n=2041) of first-line bevacizumab (Bev) plus taxane-based chemotherapy (CT) for locally recurrent or metastatic breast cancer (LR/mBC): updated results of MO19391. Eur J Cancer Suppl 2009; 7(2): 265.

2. Smith I et al. Primary analysis of study MO19391, an open-label safety study of bevacizumab plus taxane-based therapy as first-line treatment of patients with

locally recurrent (LR) or metastatic breast cancer (mBC). Cancer Res 2009; 69(Suppl): (2)292s, Abstract 4118.

3. Biganzoli L et al. Tolerability and efficacy of First-line bevacizumab (B) plus chemotherapy (CT) in elderly patients with advanced breast cancer (aBC): subpopulation analysis of the MO19391 study. J Clin Oncol 2009; 27:15s (suppl), Abstract 1032.

4. Pierga J et al. Safety and efficacy of 1st-line bevacizumab (B) plus chemotherapy (CT) for locally recurrent or metastatic breast cancer (LR/mBC): analysis of MO19391 according to CT. J Clin Oncol 2009; 27:15s(suppl), Abstract 1033 and Oral Presentation.

5. Pierga J et al. MO19391: an open-label safety study of bevacizumab plus taxane-based therapy as first-line treatment of patients with locally recurrent (LR) or metastatic breast cancer (MBC). J Clin Oncol 2008; 26(May 20 Suppl):76s, Abstract 1140.

6. Smith I et al. MO19391: an open-label safety study of bevacizumab plus taxane monotherapy or in combination as first-line treatment of patients with locally recurrent or metastatic breast cancer (LR or MBC). Eur J Cancer Suppl 2007; 7: 221, Abstract 2123.

7. Thomssen C et al. First-Line bevacizumab (Bev) combination therapy in triple-negative (TN) locally recurrent/metastatic breast cancer (LR/MBC): subpopulation analysis of study MO19391 in >2000 patients (Pts). Cancer Res 2009; 69: 851s, Abstract 6093.

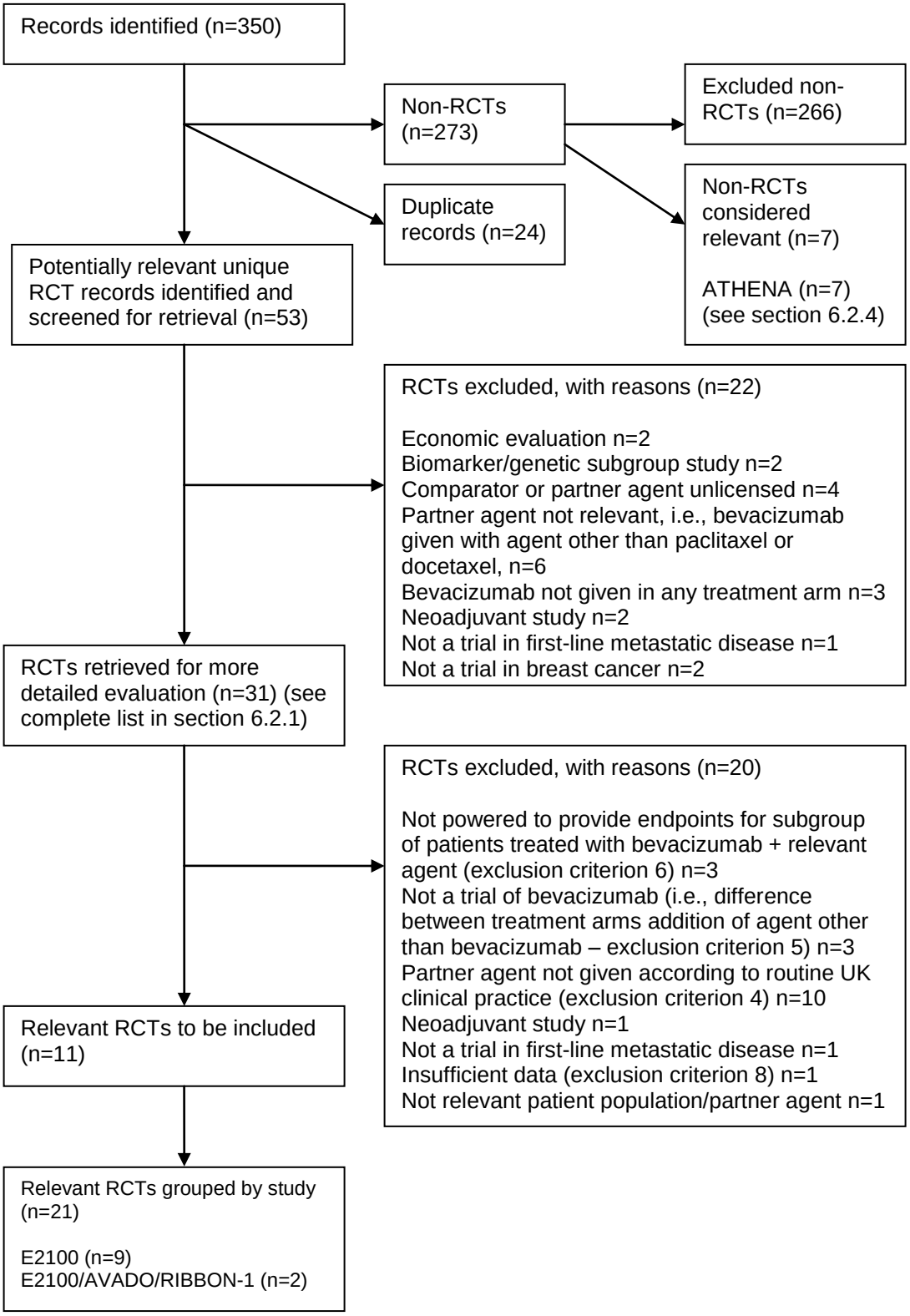
An additional reference relating to this study was identified after both the original searches and updated searches were conducted. This paper is not in the public domain but has been submitted to the *Journal of Clinical Oncology* for publication. The manuscript has been provided with the permission of the lead author for the purpose of the current submission.

Smith I et al. First-line bevacizumab plus taxane-based chemotherapy for locally recurrent or metastatic breast cancer: safety and efficacy in an open-label study in 2,251 patients. [Submitted to J Clin Oncol 2010].

6.2.5 Ongoing studies

The searches conducted did not reveal any ongoing RCTs or relevant non-RCTs investigating the use of bevacizumab in combination with paclitaxel or docetaxel in the first-line treatment of metastatic breast cancer. Roche are not aware of any ongoing studies relevant to the decision problem.

Figure 1. Flow diagram of number of studies included and excluded at each stage.



6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

Study E2100: A Randomized Phase III Trial of Paclitaxel Versus Paclitaxel Plus Bevacizumab (rhuMAb VEGF) as First-Line Therapy for Locally Recurrent or Metastatic Breast Cancer.

The primary objective of the open-label Phase III study E2100 was to evaluate the efficacy of paclitaxel in combination with bevacizumab compared with paclitaxel alone, in patients with chemotherapy-naïve locally recurrent or metastatic breast cancer. The study was sponsored and the data owned by the US Eastern Cooperative Oncology Group (ECOG). The data were passed to Genentech, who undertook the analyses presented in this submission.

Study E2100 was a Phase III, multicentre, randomised, open-label, controlled trial that evaluated the efficacy and safety of bevacizumab given in combination with paclitaxel chemotherapy to patients with locally recurrent or metastatic breast cancer, versus paclitaxel chemotherapy alone.

Randomisation to treatment arms was performed by the ECOG Coordinating Centre. After obtaining informed consent and establishing eligibility, patients were randomly assigned in a 1:1 ratio to paclitaxel + bevacizumab or paclitaxel alone. The randomisation was stratified by disease-free interval (≤ 24, > 24 months), number of metastatic sites (< 3, ≥ 3), prior receipt of adjuvant chemotherapy (yes, no) and ER status (positive, negative and unknown).

Protocol therapy was given in repeating 4-week cycles until disease progression, as assessed by the investigator, or unacceptable toxicity. All patients were given intravenous (IV) paclitaxel (90 mg/m^2 over 1 hour) once a week for 3 weeks, with no treatment given at week 4. Patients in the paclitaxel plus bevacizumab arm received IV

bevacizumab (10mg/kg) every 2 weeks, until progression of disease or unacceptable toxicity. There was no limit as to the number of cycles of protocol therapy allowed.

Patients in the paclitaxel plus bevacizumab arm who discontinued paclitaxel prior to progression were allowed to continue single-agent bevacizumab until disease progression. Similarly, they were allowed to continue single-agent paclitaxel if they discontinued bevacizumab prior to progression.

All patients were followed for response by physical and radiographic examinations (scans or X-rays) until progressive disease (PD), whether or not study therapy was discontinued prior to disease progression and for survival for 5 years from the date of randomisation.

6.3.2 Participants

Patients were included in this trial if they were ≥18 years of age, had histologically or cytologically confirmed adenocarcinoma of the breast, an ECOG performance status (PS) of 0 or 1, and were HER2-negative (unless they had received prior therapy with Herceptin® (trastuzumab)). Patients who had received prior chemotherapy for locally recurrent or metastatic breast cancer, adjuvant or neoadjuvant taxane therapy within 12 months prior to randomisation, or other adjuvant chemotherapy within three weeks prior to study entry, were excluded from the study (prior hormonal therapy for locally recurrent or metastatic disease was allowed if discontinued ≥3 weeks prior to study entry). Patients were also excluded if they had a history or radiologic evidence of CNS metastases, a history of seizure or cerebrovascular accident, bleeding diathesis, deep vein thrombosis or pulmonary embolism, or clinically significant cardiovascular disease, including myocardial infarction within 12 months prior to randomisation, unstable angina, Grade ≥2 peripheral vascular disease, uncontrolled congestive heart failure, or uncontrolled hypertension.

Table 13. Baseline characteristics of patients in study E2100.

	Paclitaxel (n=354)	Bevacizumab+ paclitaxel (n=368)
Median age, years (range)	55.0 (27–85)	56.0 (29–84)
Premenopausal or age <50, n (%)	83 (23.4)	92 (25.0)
Race/ethnicity Caucasian, n (%)	266 (75.1)	284 (77.2)
Locally recurrent disease, n (%)	4 (1.1)	8 (2.2)
ER(+), n (%)	223 (63.0)	223 (60.6)
PR(+), n (%)	158 (44.6)	166 (45.1)
HER2(+), n (%)	6 (1.7)	9 (2.4)
ER-/PR-/HER2-, n (%)	110 (31.1)	122 (33.2)
Disease-free interval, n (%) ≤24 months >24 months	 146 (41.2) 208 (58.8)	 150 (40.8) 218 (59.2)
Number of metastatic sites, n (%) <3 ≥3	 252 (71.2) 102 (28.8)	 262 (71.2) 106 (28.8)
Prior adjuvant chemotherapy, n (%)	231 (65.3)	244 (66.3)
Prior taxane therapy, n (%)	68 (19.2)	71 (20.1)
Prior anthracycline therapy, n (%)	180 (50.8)	184 (50.0)

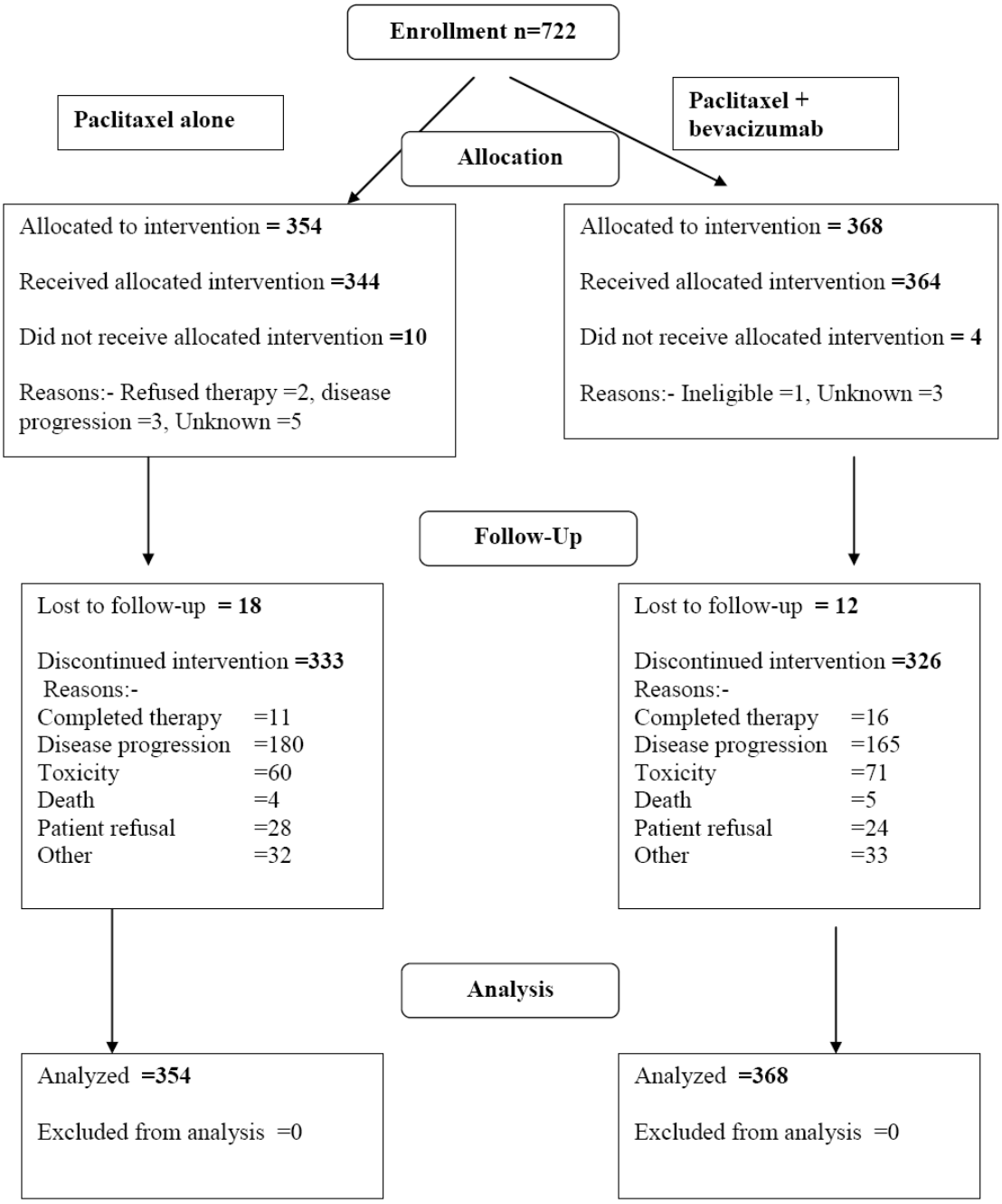
ER: Oestrogen receptor; PR; Progesterone-receptor.

The baseline characteristics of the patients in the study are shown in Table 13. The demographic and baseline characteristics were comparable across the two treatment arms. The majority of patients (~ 98%) in both treatment arms had metastatic disease, and approximately 29% of patients in each arm had ≥3 metastatic sites. The two arms were well balanced with regard to HER2 receptor status, number of involved sites, sites of involvement and tumour burden, as measured by the sum of the longest diameters of target lesions. Overall, the most frequently involved metastatic sites in both treatment arms were bone (~ 55%), lung (~ 42%) and liver (~ 42%). The majority of patients enrolled were oestrogen receptor (ER) positive (~ 62%) and approximately half (45%) were progesterone receptor (PR) positive. Just under a third of the patients (32%) had triple-negative (ER-/PR-/HER2-negative) disease. Approximately 66% of patients in each treatment arm had received adjuvant chemotherapy, 50% prior anthracycline therapy and 20% prior taxane therapy.

6.3.3 Patient numbers

The protocol specified the enrolment of approximately 685 patients who had not previously received chemotherapy for their locally recurrent or metastatic disease. The numbers enrolled are presented in a CONSORT flow chart (Figure 2). They demonstrate that the analyses of the E2100 study have been performed on an intention to treat (ITT) basis. At the time of this analysis most patients had discontinued randomised therapy, for over half the patients this was because of disease progression, while about one fifth of patients withdrew from the study because of toxicity. A total of 30 of the 722 patients were lost to follow-up.

Figure 2. Consort flow diagram of patients in study E2100.



6.3.4 Outcomes

The primary efficacy endpoint was duration of progression-free survival (PFS). Secondary endpoints were overall survival (OS), objective response (complete response [CR] and partial response [PR]) rate, duration of response and QoL. Disease progression and tumour response were assessed by the investigator and confirmed by ECOG (based on an unblinded review of data submitted by the investigator), by RECIST criteria, on X-rays or CT-scans Subsequently, the scans were collected and sent to an independent review facility (RadPharm) in order to provide an independent and blinded review of the results of the study and to verify the efficacy results. The independent review facility (IRF) for Study E2100 used radiologic and clinical evidence to detect tumour progression. Imaging-based evaluation by the IRF was performed by two radiologists and adjudicated by a third radiologist if necessary. An oncologist reviewed clinical data for the oncology review. He then reviewed both the radiologic and clinical evidence to make a final determination of response and progression status for each timepoint. The reviews were done in a blinded fashion.

Objective Response Rate (ORR) was defined as the occurrence of a complete or partial response according to the Response Evaluation Criteria in Solid Tumours (RECIST), confirmed by repeat assessment performed by the investigator ≥ 4 weeks after the criteria for response were first met.

Three interim analyses were planned at study intervals of 50%, 78%, and 100% of events using a one-sided O'Brien-Fleming boundary for the upper boundary and repeated confidence intervals (CIs) for the lower boundary. Each of these analyses consisted of a stratified log-rank test, where the stratification factors were disease-free interval (≤ 24 months, > 24 months) and prior adjuvant chemotherapy (yes, no). The analysis of PFS and objective response presented in this submission is based on data collected prior to Feb 9 2005, which was the clinical cutoff date for the first interim analysis. No further response data were included, as the results of this first analysis were made public and it was considered that this might produce bias in the unblinded trial. The cutoff date for OS is 21 October 2006, the date on which the 481st death

occurred, providing the full information required for the analysis of OS, as stated in the primary analysis plan.

The protocol specified that the National Cancer Institute Common Toxicity Criteria (NCI-CTC), Version 2.0, be used for toxicity and adverse event reporting. Adverse events and grade were reported every 3 months for patients on protocol therapy. Following discontinuation of protocol therapy, adverse events were collected every 3 months for patients who were < 2 years from randomisation and every 6 months for patients who were 2 to 5 years from randomisation. Additionally, certain adverse events were reported in an expedited manner to allow for timely monitoring of patient safety.

6.3.5 Statistical analysis and definition of study groups

A total of 685 patients were required to achieve approximately 85% power to detect a 33% improvement in median PFS, from an estimated 6 months in the paclitaxel alone arm to 8 months in the paclitaxel plus bevacizumab arm. This allowed for a maximum of 5% ineligible patients. This calculation was adjusted for sequential testing with interim analyses and corresponded to 546 events (100% information).

The primary efficacy analysis population was the ITT population, defined as all patients who were randomised to study treatment, irrespective of the assigned treatment actually received. The primary analysis for objective response included only patients with measurable disease at baseline; a supportive analysis for objective response rate was also performed on all randomised patients. The analyses for all other primary and secondary efficacy endpoints were based on the ITT population.

The overall Type I error rate for the two-sided test of PFS was controlled at $\alpha = 0.05$. The O'Brien-Fleming group sequential boundary function was used to adjust for sequential testing that resulted from the interim efficacy analyses through use of the α-spending function methodology of Lan and DeMets (1983). The boundary was constructed with a targeted final evaluation at 546 PFS events for the two treatment arms combined (100% information).

PFS, as assessed by the IRF, was analysed with baseline characteristics and stratification factors as reported by investigators and contained in the ECOG database. Subgroups and risk factors analysed for assessing the effect of treatment on efficacy outcomes included those defined by the four stratification variables (disease-free interval, number of metastatic sites, prior receipt of adjuvant chemotherapy and ER status) as well as demographic and baseline characteristics, such as age (< 40, 40–64, ≥ 65 years), race (White, non-White), baseline SLDs of all target lesions and HER2 expression status by FISH and IHC. In addition, other characteristics considered but not pre-specified for the subgroup analysis included prior adjuvant hormonal therapy, prior hormonal therapy for locally recurrent or metastatic breast cancer and prior taxane or anthracycline therapy.

Secondary efficacy endpoints included OS, ORR and duration of objective response. For each of these secondary efficacy endpoints, the paclitaxel plus bevacizumab arm and the paclitaxel alone arm were compared at the Type I error rate of $\alpha = 0.05$. To protect the study-wise error rate, a hierarchical procedure was used for testing the hypotheses associated with PFS and objective response rate.

The analysis of OS used a two-sided stratified log-rank test comparing the paclitaxel plus bevacizumab arm and the paclitaxel alone arm. The stratification factors were those used for patient randomisation (see above). Kaplan-Meier methodology was used to estimate median OS for each treatment arm. In addition, an unplanned analysis of 1-year survival was also performed. The final analysis for OS is planned to occur after 481 deaths are reported.

ORRs were formally compared between the paclitaxel plus bevacizumab arm and the paclitaxel alone arm using the Cochran-Mantel-Haenszel test, stratified for the randomisation factors (see above). Duration of objective response was estimated using Kaplan-Meier methodology.

Safety Analyses

The safety analyses included all patients who received any amount of protocol therapy. Patients were grouped according to the treatment actually received. Study treatment exposure was determined by number of therapy cycles received and number of paclitaxel and/or bevacizumab doses received. The incidence of Grade 3–5 non-hematologic adverse events and Grade 4 and 5 hematologic adverse events was summarized by treatment arm and grade using NCI-CTC terminology.

Quality of Life (FACT-B)

Quality of life was measured by the FACT-B, an instrument specifically designed for use among breast cancer patients. The FACT-B, Version 4, a 44 item QoL instrument which consists of the following five subscales:

- Physical well-being (PWB)
- Social/family well-being (SWB)
- Emotional well-being (EWB)
- Functional well-being (FWB)
- Breast cancer-specific well-being (BCS)

The difference in overall health-related QoL was assessed by the FACT-B Trial Outcome Index (TOI). The TOI is the sum of the PWB, FWB, and BCS of the FACT-B questionnaire (23 items). Each item is answered on a 5-point Likert scale from 0 to 4, with the summation of responses. In all FACT-B summary scores, including TOI, a high score indicate a good QoL. Negatively framed statements were reversed after scoring, according to manual instructions for version 4 of the functional assessments system (Brady *et al.* 1997).

The FACT-B scale is appropriate for use in oncology clinical trials, as well as in clinical practice. It demonstrates ease of administration, brevity, reliability, validity, and sensitivity to change. The test was administered and scored in accordance with manual instructions for the version 4 of the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system

The self reporting FACT-B questionnaire, consisting of a 28 item generic core plus 12 items specific for breast cancer, was completed within two weeks prior to starting treatment, and on Day 1 of weeks 17 and 33, even if treatment was delayed or the patient was removed from treatment because of disease progression or toxicity.

Each of the five subscale scores of the FACT-B, the sum PWB + FWB + BCS (Trial Outcome Index (TOI-B), and the FACT-B total score (TOT-B) was calculated for each patient at each of the three evaluations (Baseline, week 17 and week 33).

Patients without a QoL assessment at baseline were not included in any of the QoL analyses. For analysis purposes, the scores and imputation rules specified in the E2100 Statistical Analysis Plan were inverted. Thus, higher scores were better and lower scores were worse. If QoL scores were missing at either week 17 or week 33 the score was not imputed and the patient was not included in the QoL analysis for that respective time point except when disease progression or death was recorded earlier. For those patients who died or had disease progression, a value of zero (i.e., the worst score) for each of the five subscales was used for imputation. Imputation of data allowed the inclusion of a fairly substantial number of patients with missing assessments, i.e., those who died or had disease progression prior to the scheduled QoL assessment, in the analysis, thus making the analysis more meaningful.

The primary protocol specified analysis was the change from baseline for TOI-B (with imputed values) for patients in each treatment arm at week 17. The week 33 measurement for TOI-B was considered as a secondary QoL analysis, as was the week 17 and week 33 change from baseline values of the FACT-B total score (TOT-B). Additional analyses were conducted for all scales without imputed values.
For the primary analysis of change in TOI-B from baseline to week 17, the presence of a treatment effect corresponding to a difference in the change from baseline in TOI-B for the paclitaxel plus bevacizumab arm and the change from baseline in TOI-B for the paclitaxel alone arm was evaluated using the Wilcoxon rank-sum test. Secondary analyses were evaluated using the same testing procedure and methodology.

6.3.6 Critical appraisal of relevant RCTs

The sample size for this study was justified adequately:- a total of 685 patients were required to achieve approximately 85% power to detect a 33% improvement in median PFS. Follow-up was adequate for a metastatic breast cancer population, as all patients were followed-up until disease progression and then followed until death, or 5 years after randomisation. The two study groups were comparable and the statistical analyses used were appropriate for this type and size of study.

The patients were randomised centrally by the ECOG Coordinating Center and treatment allocation was then communicated to each recruiting centre. However study E2100 was an open-label study, where patients in the paclitaxel arm received no placebo infusion and so the randomised treatment was not concealed from either patient or investigator. The initial assessment of response and relapse was undertaken by the investigator, based on radiological scans of measurable lesions.

In order to eliminate any potential bias in such assessments, an independent review of radiological images/scans was carried out, with the aim of reviewing data from all 722 patients who were enrolled into the E2100 study. The study sites sent the scans to an independent review facility (RadPharm). The review consisted of Primary Review of radiographic images by radiologists, and subsequent oncological review by a RadPharm oncologist. Both assessments were carefully and completely blinded to the treatment received by the study subject. All images were reviewed and response assessed using modified RECIST criteria

The study was not undertaken in the UK and over 90% of patients entered the study in the USA, with the reminder being recruited in centres in South Africa, Canada, Peru and Sweden. In general the clinical practice in these centres will be similar to that in the UK and the background chemotherapy used in the trial is often used in this setting in the UK.

The baseline characteristics of the patients in this study show them to have similar demographics to the first-line metastatic breast cancer population in the UK, except that

HER2-positive patients were excluded from the study. There is no reason to believe that the breast cancer disease process in the study patients differed from that in patients in routine UK clinical practice. The stratification factors used in patient randomisation, which included three prognostic variables (disease free interval, number of metastatic sites and ER status) and one prior therapy variable (prior adjuvant chemotherapy), were appropriate for the treatment of a first-line metastatic breast cancer population in the UK.

In UK clinical practice paclitaxel administration may be halted after six cycles or 6 months, in the absence of disease progression, to spare patients further toxicity. Patients in the E2100 study were intended to receive weekly paclitaxel until disease progression. However, a proportion of patients were withdrawn from paclitaxel therapy before progression, due to toxicity. In the combination therapy arm, such patients continued to receive bevacizumab until disease progression. These patients therefore resemble those in the UK who receive paclitaxel for a limited duration.

The dosage regimen for bevacizumab used in this study was that detailed in the Summary of Product Characteristics, which recommends a dose of 10mg/kg body weight q2w or 15mg/kg body weight q3w.

6.4 Results of the relevant comparative RCTs

Study E2100; history of the results

The results from the planned first interim analysis of this study, with Investigator determined assessment of patient outcomes, were published (Miller *et al.* 2005; Zon *et al.* 2006; Scott 2007) and formed the basis for the initial licensed indication for Avastin in breast cancer. However, at the time the UK license was granted (March 2007), Roche agreed with the licensing authorities to provide an independent and blinded review of all 722 patients, conducted by an independent review facility, in order to verify the efficacy results. During the retrospective process of scan collection and central review of data from the study sites, the study database was updated and new efficacy and safety analyses conducted. These updated IRF data were submitted to the licensing authority,

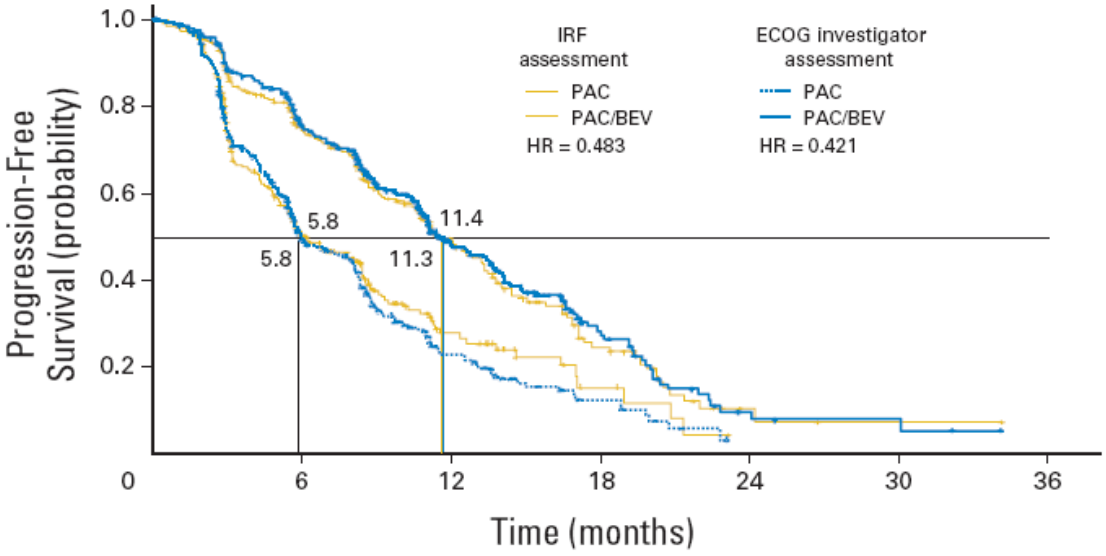
appear in the Summary of Product Characteristics and will be presented below (Cameron 2008, Gray *et al.* 2009).

Results; primary endpoint

A total of 722 patients with chemotherapy-naïve locally recurrent or metastatic breast cancer were randomised to the two treatment arms; 354 to paclitaxel alone and 368 to paclitaxel plus bevacizumab. Among the 722 randomised patients, 357 IRF-reviewed progression events had occurred in the two treatment arms (184 for the paclitaxel alone arm and 173 for the paclitaxel + bevacizumab arm), including 18 on-study deaths in the paclitaxel alone arm and 15 in the paclitaxel + bevacizumab arm. Only twelve locally recurrent patients were included in the study; four were treated with paclitaxel alone (median PFS not recorded). For the eight patients treated with paclitaxel plus bevacizumab, the median PFS was 10.9 months. No other endpoint was recorded separately for locally recurrent and metastatic patients.

A stratified analysis of the primary endpoint of progression free survival (PFS) for all randomised patients demonstrated a statistically significant and clinically meaningful increase in median PFS, from 5.8 months in the paclitaxel alone arm to 11.3 months in the paclitaxel + bevacizumab arm. The stratified hazard ratio (HR) for the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.48 (95% CI 0.39, 0.61; $p<0.0001$), demonstrating that addition of bevacizumab to paclitaxel halved the relative risk of progression. In the Kaplan-Meier graph for PFS is shown in Figure 3; the wide separation of the curves from an early time in the study suggests that all patients gained benefit from the addition of bevacizumab, whether they had a rapidly or a more slowly progressing tumour.

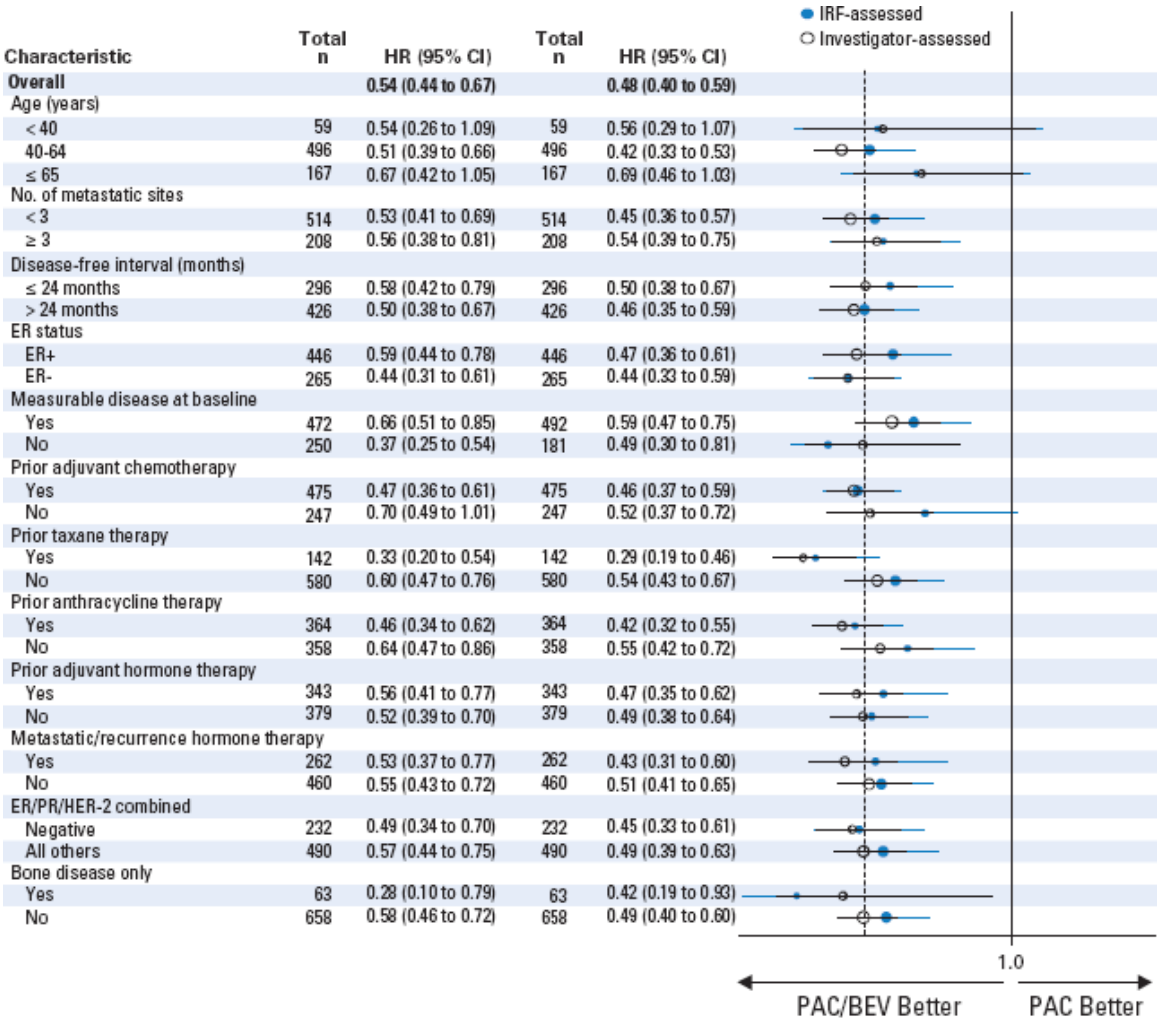
Figure 3. Progression-free survival: Randomised patients.



Results in Subpopulations; PFS by Baseline Characteristics

As shown in Figure 4, reduction in the risk of progression or death within clinically important patient subgroups was generally consistent with the overall treatment effect. Patients derived PFS benefit irrespective of prior therapy (anthracyclines or taxanes), disease-free interval, disease sites, tumour burden quantified by size of target lesions in patients with measurable disease, or hormone receptor status.

Figure 4. Analysis of progression-free survival in subpopulations.



Characteristic	Total n	HR (95% CI)	Total n	HR (95% CI)
Overall		**0.54 (0.44 to 0.67)**		**0.48 (0.40 to 0.59)**
Age (years)				
< 40	59	0.54 (0.26 to 1.09)	59	0.56 (0.29 to 1.07)
40-64	496	0.51 (0.39 to 0.66)	496	0.42 (0.33 to 0.53)
≤ 65	167	0.67 (0.42 to 1.05)	167	0.69 (0.46 to 1.03)
No. of metastatic sites				
< 3	514	0.53 (0.41 to 0.69)	514	0.45 (0.36 to 0.57)
≥ 3	208	0.56 (0.38 to 0.81)	208	0.54 (0.39 to 0.75)
Disease-free interval (months)				
≤ 24 months	296	0.58 (0.42 to 0.79)	296	0.50 (0.38 to 0.67)
> 24 months	426	0.50 (0.38 to 0.67)	426	0.46 (0.35 to 0.59)
ER status				
ER+	446	0.59 (0.44 to 0.78)	446	0.47 (0.36 to 0.61)
ER-	265	0.44 (0.31 to 0.61)	265	0.44 (0.33 to 0.59)
Measurable disease at baseline				
Yes	472	0.66 (0.51 to 0.85)	492	0.59 (0.47 to 0.75)
No	250	0.37 (0.25 to 0.54)	181	0.49 (0.30 to 0.81)
Prior adjuvant chemotherapy				
Yes	475	0.47 (0.36 to 0.61)	475	0.46 (0.37 to 0.59)
No	247	0.70 (0.49 to 1.01)	247	0.52 (0.37 to 0.72)
Prior taxane therapy				
Yes	142	0.33 (0.20 to 0.54)	142	0.29 (0.19 to 0.46)
No	580	0.60 (0.47 to 0.76)	580	0.54 (0.43 to 0.67)
Prior anthracycline therapy				
Yes	364	0.46 (0.34 to 0.62)	364	0.42 (0.32 to 0.55)
No	358	0.64 (0.47 to 0.86)	358	0.55 (0.42 to 0.72)
Prior adjuvant hormone therapy				
Yes	343	0.56 (0.41 to 0.77)	343	0.47 (0.35 to 0.62)
No	379	0.52 (0.39 to 0.70)	379	0.49 (0.38 to 0.64)
Metastatic/recurrence hormone therapy				
Yes	262	0.53 (0.37 to 0.77)	262	0.43 (0.31 to 0.60)
No	460	0.55 (0.43 to 0.72)	460	0.51 (0.41 to 0.65)
ER/PR/HER-2 combined				
Negative	232	0.49 (0.34 to 0.70)	232	0.45 (0.33 to 0.61)
All others	490	0.57 (0.44 to 0.75)	490	0.49 (0.39 to 0.63)
Bone disease only				
Yes	63	0.28 (0.10 to 0.79)	63	0.42 (0.19 to 0.93)
No	658	0.58 (0.46 to 0.72)	658	0.49 (0.40 to 0.60)

For the ITT population, the IRF-assessed unstratified HR for PFS was 0.54 (95% CI 0.44-0.67). In the subgroups which might be expected to cover patients of poor prognosis, the addition of bevacizumab to paclitaxel appeared to give somewhat greater benefit.

- The unstratified HR for the 265 ER-negative patients was 0.44 (95% CI 0.31-0.61), with an improvement from 4.9 to 11.1 months in median PFS.

- For the 232 triple-negative (TN) patients (ER-/PR-/HER2-negative) the HR for PFS was 0.49 (95% CI 0.34-0.70), with an improvement in median PFS from 5.3 to 10.6 months
- The 142 patients given prior adjuvant taxane therapy had a HR of 0.33 (95% CI 0.20-0.54) with an improvement in median PFS from 5.8 to 13.1 months.

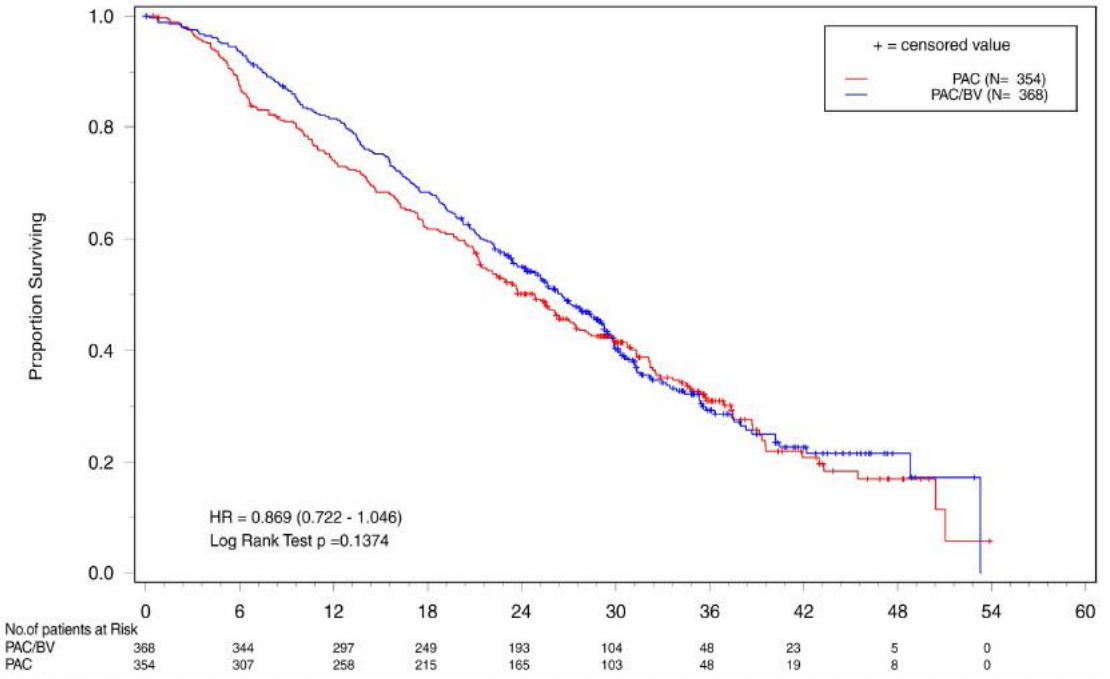
Secondary endpoints:-

Overall survival

The final analysis of OS was conducted after a total of 481 patients had died. This resulted in a data cut-off on 21 October 2006, with 238 patient deaths in the paclitaxel alone arm and 243 patient deaths in the paclitaxel + bevacizumab arm. The median OS was improved by 1.7 months, from 24.8 months with paclitaxel alone to 26.5 months with paclitaxel + bevacizumab. The stratified HR for OS in the paclitaxel + bevacizumab arm relative to the paclitaxel alone arm was 0.87 (95% CI 0.72, 1.05; p=0.14), indicating a 13% improvement in OS with the combination therapy. Kaplan-Meier curves for OS are shown in Figure 5.

No information was collected regarding subsequent therapy after disease progression for any patient. Thus, the effect of post-progression therapy (including bevacizumab) on OS could not be analysed. This may be of particular importance for the patients who received paclitaxel alone in this open-label study, once the results of the interim analysis showing a highly significant improvement in PFS in the combination arm, were made public in April 2005.

Figure 5. Overall survival: Randomised patients.



BV: Bevacizumab; PAC: Paclitaxel.

The Kaplan-Meier curves in Figure 5 separate over the first 18 months of therapy, before approaching each other at later times. A post-hoc analysis showed that the 1-year survival rate in this study was 81.4% with bevacizumab plus paclitaxel, compared with 74.0% with paclitaxel alone (p=0.017). The 7.4% absolute improvement in OS at 1 year (a 10% relative improvement in OS) reflects a possible survival benefit amongst the patients with the poorest prognosis, who had the least opportunity to receive second and third-line therapies, or to crossover to bevacizumab from the paclitaxel alone arm of the study. This view is reinforced by subgroup data, which show that median OS for ER negative patients was only 16.0 months with paclitaxel alone, compared with 20.3 months with paclitaxel plus bevacizumab (HR 0.86, 95% CI 0.65–1.13) and for triple-negative patients OS was 16.3 months in the paclitaxel arm, compared with 20.5 months in the paclitaxel plus bevacizumab arm (HR 0.89, 95% CI 0.66–1.19). Amongst patients previously treated with adjuvant taxane, median OS increased from 17.6 months with

paclitaxel alone to 26.3 months with paclitaxel plus bevacizumab (HR 0.67, 95% CI 0.45–0.99).

Time to treatment failure

Time to treatment failure (TTF) was defined as the time from randomisation to disease progression by IRF, death from any cause, discontinuation of treatment due to toxicity, discontinuation for symptomatic deterioration, or initiation of another anti-cancer therapy. This endpoint reflects most accurately the actual duration of randomised therapy for the study patients. Amongst the ITT population, the median time to treatment failure was 4.9 months with paclitaxel alone and 8.3 months with paclitaxel plus bevacizumab (HR 0.52, 95% CI 0.43–0.63). TTF was not determined for the various subgroups of patients.

Objective response rate

Among patients with measurable disease at baseline (243 patients in the paclitaxel alone arm and 229 in the paclitaxel + bevacizumab arm), the ORR was more than twice as high in the paclitaxel + bevacizumab arm (49.8%) compared with the paclitaxel alone arm (22.2%) ($p<0.0001$). Thus half the patients in the bevacizumab plus paclitaxel arm had an objective response. The results are shown in Table 14.

Table 14. Objective response based on IRF assessment: Randomised patients with measurable disease at baseline.

	PAC (n=243)	PAC/BV (n=229)
No. of patients with measurable disease at baseline	243	229
No. of patients with objective response (%)	54 (22.2%)	114 (49.8%)
Best objective response		
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	114 (49.8%)
(PAC/BV – PAC)	27.6%	
95% CI	(19.2%, 35.9%)	
Unstratified analysis		
p-value	< 0.0001	
Stratified analysis		
p-value	< 0.0001	

BV: Bevacizumab; PAC: Paclitaxel.

This large improvement in ORR was also seen amongst patient subgroups, with the ORR for the 188 ER negative patients with measurable disease being 20.0% with paclitaxel alone and 44.1% with paclitaxel plus bevacizumab. For the 167 triple-negative patients ORR increased from 21.7% with paclitaxel alone to 42.9% with paclitaxel plus bevacizumab. In the group of 90 patients with measurable disease given prior adjuvant taxane therapy, objective response rate increased from 20.9% with paclitaxel alone to 51.1% with taxane plus bevacizumab, representing an increase of 30% in the ORR with the addition of bevacizumab.

As shown in Table 15, all the IRF-assessed objective responses reported were partial responses. An additional third of the patients in the combination arm and 44% of those in the paclitaxel alone arm had stable disease. Progressive disease was seen in a quarter of the patients given paclitaxel alone, but in only 12% of patients given the combination.

Table 15. Best overall response as per IRF: Randomised patients with measurable disease at baseline.

Best Overall Response	PAC (n=243)	PAC/BV (n=229)
Complete response	0 (0.0%)	0 (0.0%)
Partial response	54 (22.2%)	114 (49.8%)
Stable disease	106 (43.6%)	77 (33.6%)
Progressive disease	62 (25.5%)	27 (11.8%)
Unable to evaluate	21 (8.6%)	11 (4.8%)

BV: Bevacizumab; PAC: Paclitaxel.

Agreement between Investigator-determined and Independently reviewed (IRF)-Based Assessments

Table 16 shows that the clinically meaningful and statistically significant benefit in PFS and ORR with the addition of bevacizumab to paclitaxel chemotherapy was demonstrated by both investigator-determined and IRF analyses and was consistent between the investigator/ECOG-based analysis (HR=0.42) and the IRF-based analysis (HR=0.48).

Table 16. Select endpoints based on ECOG/Investigator review & IRF assessment

	ECOG Review		IRF Assessment	
	PAC (n=354)	PAC/BV (n=368)	PAC (n=354)	PAC/BV (n=368)
PFS				
No. of patients with a PFS event	244	201	184	173
Median PFS (months)	5.8	11.4	5.8	11.3
Stratified log-rank test				
HR (95% CI)	0.421 (0.343, 0.516)		0.483 (0.385, 0.607)	
p-value	<0.0001		<0.0001	
Objective response rate [a]				
% of patients with an objective response	23.4	48.0	22.2	49.8
Difference in rates (95% CI)	24.6 (16.6, 32.5)		27.6 (19.2, 35.9)	
p-value	<0.0001		<0.0001	

BV: Bevacizumab; PAC: Paclitaxel.

Summary of efficacy; study E2100

The IRF data from the E2100 study show that for the ITT population, addition of bevacizumab to weekly paclitaxel came close to doubling the median PFS, with a halving of the relative risk of progression. Moreover the response rate was also more than doubled and half of all the patients had an objective response to the combination therapy. The level of increase in median PFS, decrease in the risk of progression and increase in response rate seen with the addition of bevacizumab to paclitaxel in this study, is an unprecedented improvement in efficacy over a gold-standard agent in the treatment of metastatic, HER2-negative breast cancer.

The median PFS of 5.8 months seen with paclitaxel alone compares closely with values previously reported in Phase III RCTs for single agent paclitaxel and docetaxel (Table 1, Table 3). The PFS of 11.3 months seen when bevacizumab was added to paclitaxel in

E2100, exceeds any PFS previously reported in Phase III trials of taxane mono or combination therapy in HER2-negative patients.

The ORR of 22% for weekly paclitaxel in the E2100 study was lower than in previous reports for single-agent paclitaxel given q3w (25–34%) or qw (40–42%). However, the dosing regimen in the E2100 study (90 mg/m^2 for 3 weeks out of every 4) gave a lower relative dose-intensity (67.5 mg/m^2 qw) than previous studies of weekly paclitaxel (80 or 90 mg/m^2 qw) and this may have affected the ORR.

Notwithstanding this low level of response to the background chemotherapy, the 49.8% ORR for bevacizumab plus paclitaxel in E2100 exceeds the response rates found in any previous studies of paclitaxel as a single agent or in combination therapy.

The greater than 2 years' median OS for both arms of the E2100 study is similar to that previously shown for weekly paclitaxel (24 months) but exceeds the OS found in all other Phase III studies of metastatic patients treated with chemotherapy, even in first-line studies. Overall, there was not a significant difference in OS between the study arms in E2100. However, the number of patients from the paclitaxel arm of this open label study who crossed-over to receive bevacizumab after progression was not recorded. The early publication of data demonstrating a significant PFS benefit for bevacizumab in E2100 may have increased the likelihood of these patients, mainly recruited in the USA where the drug was already available for colorectal cancer, receiving bevacizumab after progression.

A striking feature of the OS curve (Figure 5) is the initial separation between the two arms, which resulted in a significant benefit in OS at 12 months. The 10% relative improvement in OS at 12 months (7.4% absolute improvement) represents a significant saving of lives amongst the patients with the poorest prognosis. Examination of the subgroup data suggests that the patient groups who had the shortest OS with paclitaxel alone may be those with ER- or TN disease and patients given prior adjuvant taxane therapy. The latter patients may have received adjuvant taxane because of their clinician's expectation of a poor prognosis at the time of diagnosis of early breast cancer.

Quality of Life

At baseline, 302/346 (87.3%) patients in the paclitaxel alone arm and 317/357 (88.8%) patients in the bevacizumab plus paclitaxel arm completed the QoL questionnaire.

For the primary parameter, TOI-B at week 17 (with imputed values), the mean and median score was noticeably better in the bevacizumab plus paclitaxel arm compared to the paclitaxel alone arm. However, at week 33 the difference in TOI-B score between the two treatment arms was statistically significantly different (p=0.0042) in favour of the bevacizumab plus paclitaxel arm (Table 17).

Table 17. Study E2100 Quality of Life change from baseline with imputations (randomised patients with baseline FACT-B assessments).

Visit	Treatment	Change from Baseline						
		N	Mean	SD	Median	Min	Max	p-value
Primary Analysis - Trial Outcome Index (TOI-B)								
Week 17	Pac	230	-6.4	17.0	-4.0	-78	45	0.2024
	Bev + Pac	270	-4.8	15.5	-3.0	-70	34	
Week 33	Pac	213	-16.4	25.6	-8.8	-83	52	0.0042
	Bev + Pac	235	-10.4	22.6	-5.0	-81	29	
Secondary Analysis - Total FACT-B Score (TOT-B)								
Week 17	Pac	231	-8.3	26.9	-4.0	-124	75	0.0475
	Bev + Pac	269	-4.6	23.5	-1.3	-119	49	
Week 33	Pac	215	-24.9	42.6	-9.0	-131	75	0.0046
	Bev + Pac	235	-14.5	37.0	-3.9	-132	54	

Bev: Bevacizumab; Pac: Paclitaxel.

The TOT-B score and the score for each of the five subscales showed a similar pattern. At both weeks 17 and 33, the scores were noticeably better in patients treated with bevacizumab combination therapy than in those treated with paclitaxel alone. The TOT-B score at week 17 already showed a statistically significant difference in favour of the bevacizumab plus paclitaxel arm (p=0.0475), which became even more pronounced at week 33 (p=0.0046).

Table 18. Study E2100 Quality of Life change from baseline without imputations (randomised patients with baseline FACT-B assessments).

Visit	Treatment	Change from Baseline						
		N	Mean	SD	Median	Min	Max	p-value
Trial Outcome Index (TOI-B)								
Week 17	Pac	216	-3.5	12.5	-3.0	-41	45	0.3202
	Bev + Pac	259	-2.7	11.6	-2.2	-49	34	
Week 33	Pac	162	-4.3	13.4	-5.0	-34	52	0.1903
	Bev + Pac	205	-3.3	12.7	-3.0	-54	29	
Total FACT-B Score (TOT-B)								
Week 17	Pac	217	-3.1	17.5	-2.5	-55	75	0.0818
	Bev + Pac	256	-0.8	14.5	-1.0	-56	49	
Week 33	Pac	163	-3.3	17.8	-3.0	-45	75	0.2432
	Bev + Pac	205	-1.9	17.0	-2.0	-65	54	

Bev: Bevacizumab; Pac: Paclitaxel.

Similar results were also seen for TOI-B, TOT-B, and all subscale scores at week 17 and week 33 in the changes from baseline when imputed values were not used in the analysis, and the mean scores were generally better in the bevacizumab plus paclitaxel arm than in the paclitaxel alone arm (Table 18).

Taken together, these results demonstrate that the addition of bevacizumab to paclitaxel led to a relative improvement in QoL, as measured by FACT-B, compared to treatment with paclitaxel alone. After both 17 and 33 weeks of treatment with bevacizumab plus paclitaxel, QoL scores for the primary (TOI-B) and secondary (TOT-B) analyses and for all five subscales were consistently better than those for patients treated with paclitaxel alone.

This suggests that addition of bevacizumab to paclitaxel did not add to the burden of side-effects in a way which compromised the improved QoL patients experienced when remaining progression-free for a longer time.

The QoL findings reported in study E2100 should be interpreted in the context of the main clinical efficacy results. The maintained and relatively higher QoL scores for the

two main measures, TOI-B and TOT-B, reflecting both the acceptable tolerability and the improvement in cancer outcome, i.e. prolongation in PFS, strongly suggests that patients treated with the combination of bevacizumab and paclitaxel experienced a significant and clinically meaningful benefit. Taken together the efficacy, tolerability and QoL data reported from this study, provide support for the overall clinical benefit of patients treated with bevacizumab combined with paclitaxel as compared with paclitaxel alone for the first line treatment of patients with metastatic breast cancer.

6.5 Meta-analysis

Although two phase III RCTs of the addition of bevacizumab to taxane therapy in first-line treatment of metastatic breast cancer were identified, a meta-analysis of these studies is not considered appropriate. The dosing regimen of 100mg/m^2 docetaxel q3w as given in the AVADO study, is not routinely used in NHS clinical practice, as it is associated with a significant burden of adverse events, giving a tolerability profile which UK clinicians do not regarded as appropriate in the palliative treatment of most first-line metastatic breast cancers. Docetaxel is also given for a maximum of six to eight cycles in UK practice and treatment is not extended to the nine cycles used in the AVADO study. Hospital sales data from IMS show that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles q3w, at an average planned dose of 150mg (or 79mg/m^2 for an average 1.9m^2 patient).

Weekly paclitaxel however, with its more benign toxicity profile and recent evidence of superior activity to paclitaxel q3w is growing in acceptance in the NHS. Moreover, the tolerability profile of weekly paclitaxel means that it may be given for prolonged periods of time, as in the E2100 study. These differences in dosing practice and acceptability in the UK for the two taxane regimens mean that a meta-analysis of the studies is not appropriate.

6.6 Indirect/mixed treatment comparisons

An indirect treatment comparison has been conducted to synthesize data from the required comparators that are not available in a head to head trial. In this instance, our focus is on Avastin in combination with paclitaxel compared to paclitaxel or docetaxel alone or gemcitabine in combination with paclitaxel as described in the final scope issued by NICE. As described in the Executive Summary and in section 7.3, bevacizumab in combination with docetaxel is highly unlikely to provide a more cost-effective outcome than the analysis of bevacizumab in combination with paclitaxel due to its more expensive costs.

6.6.1 Search methodology

The evidence for the indirect treatment comparison was obtained by performing a systematic review of the literature. The papers obtained are used to compare bevacizumab plus paclitaxel directly with a comparator (head-to-head evidence) and indirectly (e.g. bevacizumab plus paclitaxel may be compared with gemcitabine plus paclitaxel by combining a paper in which bevacizumab plus paclitaxel is compared with paclitaxel monotherapy and a paper in which paclitaxel monotherapy and paclitaxel plus gemcitabine are compared).

A systematic review was conducted in order to obtain all relevant information on the efficacy and safety of:

- Bevacizumab plus paclitaxel in the first-line treatment of metastatic breast cancer relative to
    - paclitaxel monotherapy
    - docetaxel monotherapy
    - gemcitabine plus paclitaxel
    - bevacizumab plus docetaxel

A systematic search of Medline, EMBASE and BIOSIS was performed for records from 1993 to the present. In addition, meeting abstracts from the American Society of Clinical Oncology (ASCO) annual conference were searched. ASCO is the leading global oncology conference and it is unusual for any significant clinical trial not to be presented here (often the first presentation). Any key clinical trial data relevant to the submission not yet published in a journal as a full paper is expected to be found here.

The search strategy is displayed in Appendix 2, section 10.2.

Searches used index and text words which included *breast cancer* or *breast neoplasms* and one of the relevant study treatments as descriptors. The search was limited to the relevant disease setting using terms including *metastatic* or *metastasis*. The search was restricted to include only documents relating to humans and clinical trials, exclude reviews, and identify randomised controlled trials wherever possible. The search was further restricted manually according to inclusion/exclusion listed below. There were no restrictions by language.

6.6.2 Identification and study selection

INCLUSION CRITERIA

The identified studies were included according to the following predetermined conditions:

1. Study design – randomised controlled trials (RCT) that may either be blinded or non-blinded and published or unpublished

2. Study population – metastatic breast cancer patients, predominantly (>50%) HER2-negative

3. Study treatment/relevant agent – at least one of the treatment arms had to use one of the following interventions: bevacizumab + paclitaxel, paclitaxel monotherapy, docetaxel monotherapy, gemcitabine + paclitaxel, or bevacizumab + docetaxel

4. Outcome measures – 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.

5. Language – no restrictions by language

EXCLUSION CRITERIA

The following exclusion criteria were manually applied:

1. Study design – retrospective studies, case reports, non-randomised trials were excluded; trials with <100 patients receiving a relevant study treatment

2. Applicability to indirect treatment comparison – studies without two treatment arms relevant to the scope issued by NICE (paclitaxel monotherapy [qw or q3w], docetaxel monotherapy, gemcitabine plus paclitaxel, bevacizumab plus paclitaxel, bevacizumab plus docetaxel) which do not provide randomised data comparing two relevant arms and therefore would not inform the present indirect treatment comparison.

3. Study population – trials where (≥60%) patients were receiving study treatment as a second or later line of therapy for their metastatic disease; trials in which patients were preselected or study group was restricted (e.g., predominantly HER2-positive or hormone receptor positive, elderly patients); trials in which the patients were anthracycline-naive and therefore eligible for anthracycline treatment (the present NICE submission refers only to patients who are ineligible to receive anthracyclines as first-line therapy for metastatic breast cancer, generally due to anthracycline exposure in the adjuvant setting)

4. Relevant disease – trials in which patients were treated in the neoadjuvant or adjuvant setting; trials in other diseases (e.g., other cancer type, ocular use of bevacizumab)

5. Study treatment/relevant agent – trials where one of the five relevant study treatments identified above was not used in at least one of the study arms; trials using

an unlicensed/experimental agent; trials where the relevant treatment was given as part of a sequential regimen with a non-relevant treatment (e.g., taxane with an anthracycline); trials where the relevant treatment was given according to an experimental regimen; trials where the relevant agent was not given according to routine UK clinical practice.

6. Outcome measure – records presenting economic analyses, biomarker/genetic studies, quality of life data (where no new efficacy data were presented), or retrospective subgroup studies of RCTs were excluded

7. Insufficient data – ongoing studies with no data available or preliminary data not sufficient for analysis (e.g., data on patient demographics/study treatment received but no efficacy data), or dose-finding studies were excluded

Extension of search strategy: paclitaxel and docetaxel regimens

Ideally, all RCTs evaluated would have been conducted only in first-line metastatic breast cancer patients. However, studies in this setting were not available for all the of the five interventions listed above, in particular paclitaxel monotherapy and docetaxel monotherapy. The exclusion criterion for the disease setting therefore specified that trials in which the majority of patients (≥60%) were being treated for second or later lines of metastatic breast cancer would be excluded.

As 3-weekly paclitaxel, weekly paclitaxel and 3-weekly docetaxel are the common interventions between the five treatments being considered, either as monotherapy or in combination with gemcitabine or bevacizumab, data comparing these three taxane regimens are particularly pertinent. A second search was therefore conducted to extend the original search beyond the setting of metastatic disease, in an attempt to identify randomised controlled trials comparing paclitaxel and docetaxel monotherapy regimens This search strategy is shown in appendix 2, section 10.2.

The inclusion/exclusion criteria detailed above for the main search strategy were applied to the extended search strategy. The criteria were the same, except for the following key differences:

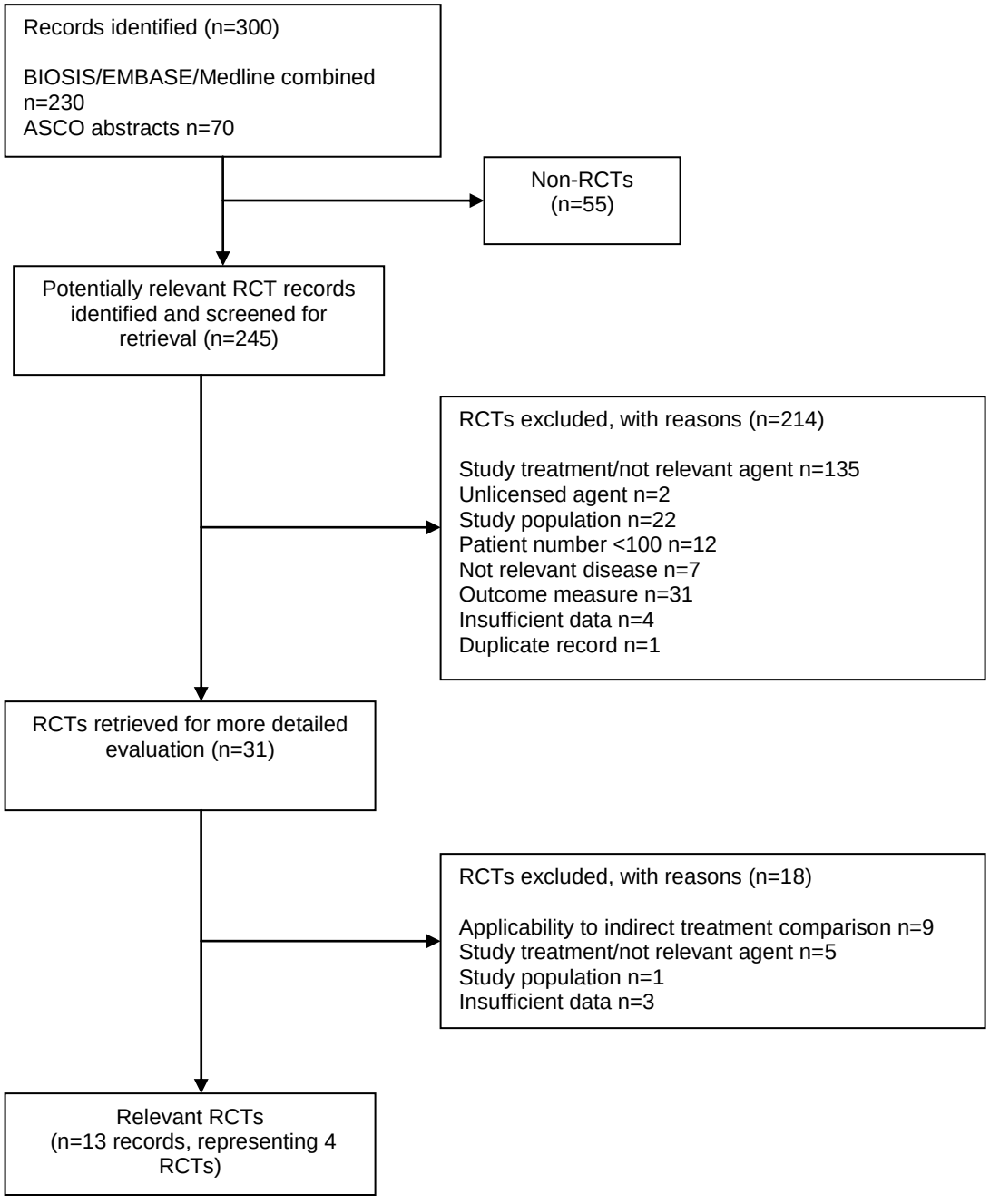
- **Study population** – the search included studies in any stage of breast cancer (i.e., not restricted to metastatic breast cancer), due to the reasons outlined above
- **Study treatment/relevant agent** – studies considered for inclusion compared at least two of the following taxane monotherapy regimens: weekly paclitaxel, 3-weekly paclitaxel, weekly docetaxel, 3-weekly docetaxel. Trials in which the relevant therapy was used as part of a neoadjuvant regimen were excluded

6.6.3 Results of search

6.6.3.1 Results of Main search

Figure 6 presents the flow chart of the search strategy. The search strategy identified a total of 300 records. Records were checked to confirm that they represented a randomised controlled trial (RCT). Abstracts for each of the RCTs were assessed for relevance. For each excluded RCT, a rationale was recorded and these are provided in the flow chart. Where more than one reason for excluding the trial could be given, the trial is listed under the main reason for exclusion in the flow chart. Where it was not possible to determine relevance from the abstract, the full record or paper was obtained and evaluated in more detail. Further trials were excluded at this stage to give the final list of relevant RCTs.

Figure 6. Flow diagram for number of studies included and excluded at each stage – main search



RCT records retrieved for detailed evaluation and excluded, with reasons

A total of 31 RCT records were retrieved in full for more detailed evaluation, 18 of which were excluded following assessment. The rationale for excluding each of these trials is presented below alongside a comprehensive list. Where more than one record was retrieved representing the same trial, these have been grouped.

1. Miles D et al. Randomised, double-blind, placebo-controlled, phase III study of bevacizumab with docetaxel or docetaxel with placebo as first-line therapy for patients with locally recurrent or metastatic breast cancer (mBC): AVADO. J Clin Oncol 2008; 26(May 20 Suppl): 43s, Abstract LBA1011 and Oral Presentation.

- Study treatment/not relevant agent – In the AVADO study, all patients were given docetaxel at a dose of 100 mg/m^2 q3w for up to nine cycles. This dosing regimen is not representative of routine NHS clinical practice, where clinicians generally treat first line metastatic breast cancer patients with docetaxel 75mg/m^2 q3w for a maximum of 6, or in exceptional cases 8, cycles. Hospital sales data from IMS show that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles q3w, at an average planned dose of 150mg (or 79mg/m^2 for an average 1.9m^2 patient). A docetaxel dose of 100mg/m^2 is associated with a significant burden of adverse events, giving a tolerability profile which UK clinicians do not regarded as appropriate in the palliative treatment of most first-line metastatic breast cancers.

2. Di Leo A et al. Phase III, double−blind, randomised study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first−line treatment for metastatic breast cancer. J Clin Oncol 2008; 26: 5544−52.

3. Di Leo A et al. Lapatinib (L) with paclitaxel compared to paclitaxel as first-line treatment for patients with metastatic breast cancer: A phase III randomised,

double-blind study of 580 patients. J Clin Oncol 2007; 25: 18S (June 20 Suppl), Abstract 1011.

- Applicability to indirect treatment comparison – This trial compared paclitaxel q3w plus lapatinib with paclitaxel q3w, and included only one treatment arm relevant to the scope issued by NICE (paclitaxel q3w). The study does not provide comparative data from two relevant arms that would inform the indirect treatment comparison, and has therefore been excluded in accordance with exclusion criterion 2.

4. Rivera E et al. Phase 3 study comparing the use of docetaxel on an every-3-week versus weekly schedule in the treatment of metastatic breast cancer. Cancer 2008; 112: 1455−61.

5. Rivera E et al. Phase III study of docetaxel weekly (DW) versus every 3 weeks (D) in patients with metastatic breast cancer: Final results. J Clin Oncol 2006; 24:18S (June 20 Suppl), Abstract 574.

- Study treatment/not relevant agent – This was a small phase III study in which 62 metastatic breast cancer patients were randomised to receive docetaxel according to the established 3-weekly regimen and 62 received docetaxel on a weekly schedule. Therefore, as the number of patients receiving the established 3-weekly regimen was less than 100 this trial was excluded, in accordance with exclusion criteria 1 and 5.

6. Khoo K et al. Gemcitabine and split−dose paclitaxel or docetaxel in metastatic breast cancer: A randomised phase II study. Eur J Cancer 2006; 42: 1797−806.

- Study treatment/not relevant agent – This three-arm phase II study aimed to compare two regimens of gemcitabine plus paclitaxel (GP1 or GP2) and gemcitabine plus docetaxel (GD) in metastatic breast cancer. The two arms of interest for the purpose of this appraisal are the gemcitabine plus paclitaxel arms

(GP1 and GP2). Gemcitabine plus paclitaxel was given in 3-weekly cycles of either: gemcitabine 1250 mg/m^2 on days 1 and 8 and paclitaxel 175 mg/m^2 on day 1 (GP1); or gemcitabine 1000 mg/m^2 on days 1 and 8 and paclitaxel 100 mg/m^2 on days 1 and 8 (GP2). According to the licensed indication for gemcitabine in breast cancer, gemcitabine 1250 mg/m^2 on days 1 and 8 should be given in combination with paclitaxel 175 mg/m^2 on day 1 of each 3-week cycle (Gemzar Summary of Product Characteristics). Therefore, the GP2 arm represents an unlicensed or experimental treatment regimen. The number of patients randomised to the GP1 arm, in which gemcitabine plus paclitaxel was given according to the licensed regimen, was less than 100 (n=72); therefore this trial was excluded, in accordance with exclusion criteria 1 and 5.

7. O'Shaughnessy J et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline−pretreated patients with advanced breast cancer: phase III trial results.

- Study population – A large proportion of patients were heavily pretreated in this trial of capecitabine plus docetaxel versus docetaxel alone. A total of 48% and 53% of patients in the capecitabine/docetaxel and docetaxel arms were receiving study therapy for second-line treatment of metastatic disease; a further 17% and 16%, respectively were being treated in the third- or fourth-line setting. As ≥60% of patients were not first-line, this trial was excluded in accordance with exclusion criterion 2.

8. Paridaens R et al. Paclitaxel versus doxorubicin as first−line single−agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer. J Clin Oncol 2000; 18: 724-33.

- Applicability to indirect treatment comparison - This study does not include two arms relevant to the scope issued by NICE and therefore would not inform the indirect treatment comparison (exclusion criterion 2). In addition, the present NICE submission refers only to patients who are ineligible to receive

anthracyclines as first-line therapy for metastatic breast cancer, generally due to anthracycline exposure in the adjuvant setting. The study population in Paridaens 2000 were able to receive anthracycline therapy and so are not representative of those patients referred to in the current submission (exclusion criterion 3). This study in an anthracycline-naive patient population is not as relevant as other paclitaxel studies which have been included for the purpose of the cross-trial comparison.

9. Smith R et al. Randomized trial of 3−hour versus 24−hour infusion of high−dose paclitaxel in patients with metastatic or locally advanced breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B−26. J Clin Oncol 1999; 17: 3403−11.

- Study treatment/not relevant agent – This trial investigated high-dose paclitaxel given at a dose of 250 mg/m^2 every 3 weeks as a 3-hour or 24-hour infusion. Standard-dose 3-weekly paclitaxel is given at a dose of 175-200 mg/m^2. This trial was excluded as paclitaxel was not given as per standard clinical practice and this would be expected to be reflected in the results.

10. Bonneterre J et al. (2002) Docetaxel vs 5-fluorouracil plus vinorelbine in metastatic breast cancer after anthracycline therapy failure. Br J Cancer; 87(11): 1210-15.

- Applicability to indirect treatment comparison - This study does not include two arms relevant to the scope issued by NICE and therefore would not inform the indirect treatment comparison (exclusion criterion 2). In addition, a total of 66% of patients had received at least one line of prior chemotherapy for metastatic disease. As ≥60% of patients were not first-line, this trial was also excluded in accordance with exclusion criterion 3.

11. Bishop J et al. Initial paclitaxel improves outcome compared with CMFP combination chemotherapy as front−line therapy in untreated metastatic breast cancer. J Clin Oncol 1999; 17: 2355−64.

12. Bishop J et al. A randomised study of paclitaxel versus cyclophosphamide/ methotrexate/5−fluorouracil/prednisone in previously untreated patients with advanced breast cancer: preliminary results. Taxol Investigational Trials Group, Australia/New Zealand. Semin Oncol 1997; 24 (5): Suppl 17, S17−5−S17−9.

- Applicability to indirect treatment comparison - This study does not include two arms relevant to the scope issued by NICE and therefore would not inform the indirect treatment comparison (exclusion criterion 2). In addition, a large proportion of patients in this trial had received no prior adjuvant chemotherapy (73%). Of those who had been treated with chemotherapy for early breast cancer, all but 3% received a CMF-based regimen. The present NICE submission refers only to patients who are ineligible to receive anthracyclines as first-line therapy for metastatic breast cancer, generally due to anthracycline exposure in the adjuvant setting (exclusion criterion 3) References 10 and 11 represent an older trial, and because clinical practice has changed this anthracycline-naive patient population is not as relevant as other paclitaxel studies which have been included for the purpose of this analysis.

13. Nabholtz J et al. Prospective randomised trial of docetaxel versus mitomycin plus vinblastine in patients with metastatic breast cancer progressing despite previous anthracycline−containing chemotherapy. 304 Study Group. J Clin Oncol 1999; 17: 1413−24.

14. Nabholtz J et al. Docetaxel vs mitomycin plus vinblastine in anthracycline-resistant metastatic breast cancer. Oncol 1997; 11 (Suppl 8): 25−30.

- Applicability to indirect treatment comparison - This study does not include two arms relevant to the scope issued by NICE and therefore would not inform the

indirect treatment comparison (exclusion criterion 2). In addition, atotal of 81% of patients had received prior chemotherapy for metastatic disease. As ≥60% of patients were not first-line, this trial was also excluded in accordance with exclusion criterion 3.

15. Chan S et al. Prospective randomised trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999; 17: 2341−54.

- Applicability to indirect treatment comparison - This study does not include two arms relevant to the scope issued by NICE and therefore would not inform the indirect treatment comparison (exclusion criterion 2). In addition, one of the inclusion criteria for this trial was that all patients had to have received previous alkylating agent chemotherapy (usually CMF) either in the adjuvant setting or for advanced disease. The present NICE submission refers only to patients who are ineligible to receive anthracyclines as first-line therapy for metastatic breast cancer, generally due to anthracycline exposure in the adjuvant setting This study in an anthracycline-naive patient population is not as relevant as other docetaxel studies which have been included for the purpose of this analysis, and has also been excluded in accordance with exclusion criterion 3 on the basis of the anthracycline-naive patient population.

16. Verrill M et al. Anglo-Celtic IV: First results of a UK National Cancer Research Network randomised phase 3 pharmacogenetic trial of weekly versus 3 weekly paclitaxel in patients with locally advanced or metastatic breast cancer (ABC). J Clin Oncol 2007; 25: 18S (June 20 Suppl), LBA1005.

- Insufficient data – The first results from this study has been reported in the form of a conference abstract. Patients with prior treatment for metastatic disease were eligible for this study. As details patient demographics have not been reported it is not possible to determine how many patients were first-line metastatic breast cancer patients. In this study weekly paclitaxel was limited to 12 cycles and 3-weekly to six cycles. In the 2008 trial by Seidman which also

evaluated 3-weekly and weekly paclitaxel, treatment was continued until disease progression (as in the E2100 study of paclitaxel and bevacizumab). Therefore, Seidman 2008 provides more comprehensive and relevant data than Verrill 2007, which was excluded on this basis.

17. Hoelzer K et al. Preliminary results of a randomised phase II study of paclitaxel and bevacizumab ± gemcitabine as first-line treatment for metastatic breast cancer. J Clin Oncol 2009; 27: 15s, Abstract 1089.

18. Brufsky A et al. A phase II study of paclitaxel and bevacizumab +/-gemcitabine as first-line treatment for metastatic breast cancer (MBC): Interim safety results. J Clin Oncol 2008; 26(May 20 Suppl.): 64s, Abstract 1095.

- Insufficient data – The most recent results available from this trial include data from 119 patients, including 61 treated with paclitaxel plus bevacizumab. As the number of patients receiving the relevant treatment was less than 100 this trial was excluded, in accordance with exclusion criterion 1. In addition, this study does not include two arms relevant to the scope issued by NICE and therefore would not inform the indirect treatment comparison (exclusion criterion 2).

Complete list of relevant RCTs (records grouped by study)

See also Table 19.

E2100: Randomised phase III trial of paclitaxel versus paclitaxel plus bevacizumab for locally recurrent/metastatic breast cancer

1. Cameron D et al. Bevacizumab in the first-line treatment of metastatic breast cancer. Eur J Cancer Suppl 2008; 6: 21-28.
2. Klencke B et al. Independent review of E2100 validates progression-free survival (PFS) improvement with the addition of bevacizumab (B) to paclitaxel (P) as initial chemotherapy for metastatic breast cancer (MBC). J Clin Oncol 2008; 26(May 20 Suppl): 50s, Abstract 1036.

3. Miller K et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. New Engl J Med 2007; 357(26): 2666-76.
4. Zon R et al. A randomised phase III trial of paclitaxel with or without bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: Eastern Cooperative Oncology Group trial E2100. Eur J Cancer Suppl 2006; 4(2): 46, Abstract 7.
5. Miller K et al. First-line bevacizumab and paclitaxel in patients with locally recurrent or metastatic breast cancer: A randomised, phase III trial coordinated by the Eastern Cooperative Oncology Group (E2100). Eur J Cancer Suppl 2005; 3: 77, Abstract 275.
6. Miller K et al. A randomised phase III trial of paclitaxel versus paclitaxel plus bevacizumab as first-line therapy for locally recurrent or metastatic breast cancer: a trial coordinated by the Eastern Cooperative Oncology Group (E2100). Breast Cancer Res Treat 2005; 94(Suppl 1): S6, Abstract 3.
7. Miller K et al. E2100: a phase III trial of paclitaxel versus paclitaxel/bevacizumab for metastatic breast cancer. Clin Breast Cancer 2003; 3: 421-22.

Randomised phase III trial of paclitaxel plus gemcitabine versus paclitaxel monotherapy for metastatic breast cancer

8. Albain K et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. J Clin Oncol 2008; 26: 3950−57.
9. Albain K et al. Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. J Clin Oncol 2004; 22: 14S (July 15 Suppl), Abstract 510.

CALGB 9840: Randomised phase III trial of weekly versus 3-weekly paclitaxel for metastatic breast cancer

10. Seidman A et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2

overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008; 26: 1642−49.

11. Seidman A et al. CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour(h) infusion versus standard (S) 3h infusion every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomised for T in HER2 normal MBC. J Clin Oncol 2004; 22: 14S (July 15 Suppl), Abstract 512.

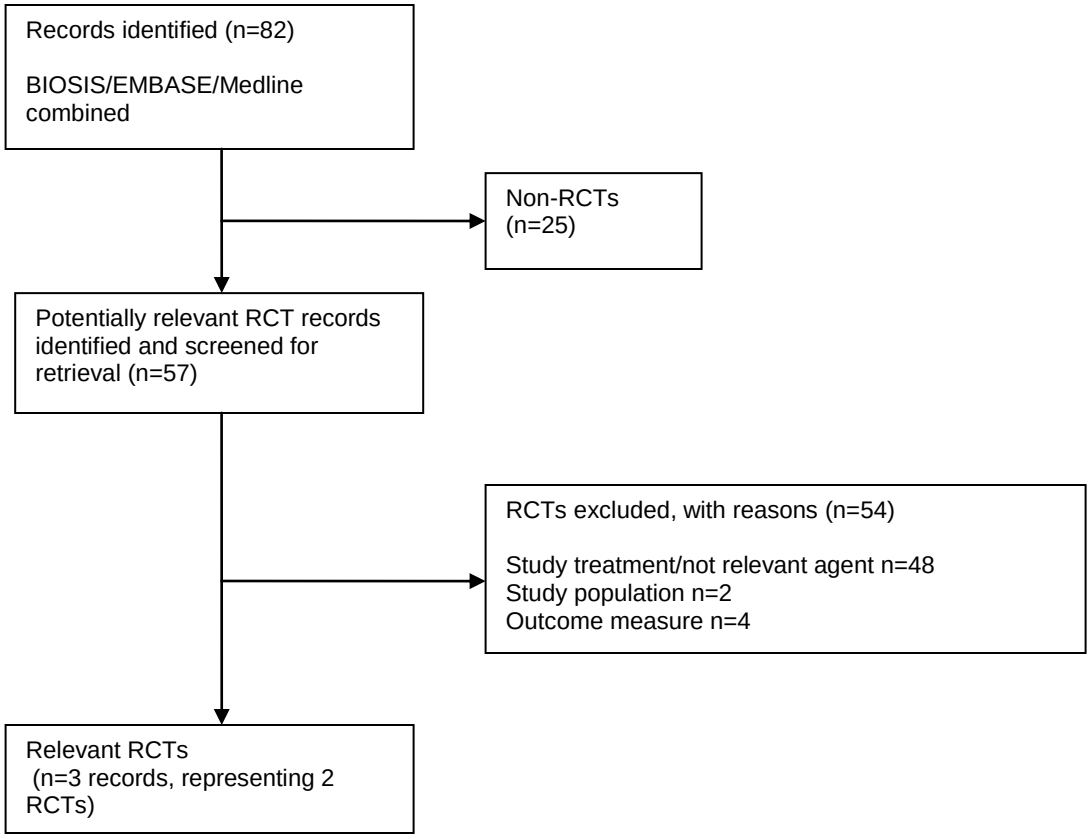
Randomised phase III trial of paclitaxel versus docetaxel for metastatic breast cancer

12. Jones S et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23: 5542−51.
13. Jones S et al. Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer. Breast Cancer Res Treat 2003; 82(Suppl 1): S9.

6.6.3.2 Results of extended search

Figure 7 presents the flow chart of the extended search strategy which aimed to identify RCTs comparing paclitaxel and docetaxel monotherapy regimens in breast cancer, not restricted to the setting of advanced disease. The search strategy identified a total of 82 records. Records were checked to confirm that they represented a randomised controlled trial (RCT). Abstracts for each of the RCTs were obtained and assessed. It was not considered necessary at this stage to obtain all records in full as all the information needed to assess relevance, according to the inclusion/exclusion criteria listed above, could be found in the contents of the abstracts. For each excluded RCT, a rationale was recorded and these are provided in the flow chart.

Figure 7. Flow diagram for number of studies included and excluded at each stage – extended search



Relevant RCTs – extended search

1. Sparano J et al. Weekly paclitaxel in the adjuvant treatment of breast cancer. New Engl J Med 2008; 358: 1663-71.
2. Jones S et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23: 5542−51.
3. Jones S et al. Randomized trial comparing docetaxel and paclitaxel in patients with metastatic breast cancer. Breast Cancer Res Treat 2003; 82(Suppl 1): S9.

Records 2 and 3 had already been identified in the original search. Therefore, the extended search strategy identified 1 unique relevant RCT record (Sparano *et al.* 2008). This study has not been included in the indirect treatment comparison, as the study was in early breast cancer patients and the present appraisal is only concerned with metastatic breast cancer patients. However, this large randomised trial of 4950 patients provides data on the taxane monotherapy regimens of interest (weekly paclitaxel, paclitaxel q3w, weekly docetaxel, docetaxel q3w) within the same trial, allowing for direct comparison of these regimens. A similar trial has not been conducted in the setting of advanced disease. In the absence of equivalent metastatic data, this adjuvant trial is therefore included for the purpose of discussion. Breast cancer is recognized as a disease continuum from the early to the advanced setting and comparable treatment efficacy has been shown for numerous agents, from tamoxifen to trastuzumab, in the early and advanced breast cancer setting.

This study compared docetaxel with paclitaxel, each drug dosed either q3w or qw, in 4950 patients with node-positive or high-risk node-negative early breast cancer. Patients all received 4 cycles of doxorubicin and cyclophosphamide q3w, followed by taxane therapy for 12 weeks, given either as 4 cycles q3w, or as 12 weekly doses. This large study in early breast cancer clearly demonstrated that docetaxel q3w and paclitaxel qw at the doses used were the most effective regimens. Paclitaxel qw gave the highest 5-year DFS and OS (81.5% and 89.7%), followed by docetaxel q3w (5-year DFS 81.2% and OS 87.3%).

In this early breast cancer study weekly paclitaxel was also associated with the lowest level of grade 3-4 adverse events. Twenty-eight percent of patients given paclitaxel qw recorded grade 3-4 adverse events, compared with 30% given paclitaxel q3w (p=0.32 vs paclitaxel qw), 71% given docetaxel q3w (p<0.001) and 45% given docetaxel qw (p<0.001).

Trials used to inform the indirect treatment comparison

Table 19 provides a summary of the remaining trials used to form a network for the indirect treatment comparison. However, some of these remaining studies are not without flaws, which are discussed below:

1. Seidman A et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. J Clin Oncol 2008; 26: 1642−49.
    - Analysis method – The Seidman trial is the most suitable trial to answer the question of the relative treatment benefit of weekly paclitaxel over 3-weekly paclitaxel in metastatic breast cancer. The other notable trial in metastatic breast cancer that attempts to answer this question is the Verrill trial already excluded for reasons described above. However, the study design and resulting analysis for the Seidman trial allowed for an imbalance of trastuzumab treated patients in the two arms and therefore the possibility of biased results.

2. Jones S et al. Randomized phase III study of docetaxel compared with paclitaxel in metastatic breast cancer. J Clin Oncol 2005; 23: 5542−51.
    - Study treatment/not relevant agent –this study uses a higher docetaxel dose and a longer duration of treatment compared with standard UK practice. Docetaxel 3-weekly was given at a dose of 100 mg/m^2 until disease progression or unacceptable toxicity, which resulted in a median

of six cycles and a maximum of 32 cycles. In routine NHS clinical practice, clinicians generally treat first-line metastatic breast cancer patients with docetaxel 75mg/m^2 q3w for a maximum of six, or in exceptional cases eight, cycles. A docetaxel dose of 100mg/m^2 is associated with a significant burden of adverse events, giving a tolerability profile which UK clinicians do not regarded as appropriate in the palliative treatment of most first-line metastatic breast cancers.

Despite the limitation of these studies, it was considered that they remain the most appropriate trials to include within the network of trials for the purposes of this indirect comparison.

6.6.4 Summary of trials used to conduct the indirect comparison

Table 19. Relevant RCTs

Trial	Intervention	Comparator	Study population	Primary study refs
E2100	Bevacizumab + paclitaxel (weekly) n=368	Paclitaxel (weekly) n=354	First-line LR/mBC	Cameron D et al. Eur J Cancer Suppl 2008; 6: 21-28. Miller K et al. New Engl J Med 2007; 357(26): 2666-76.
Albain 2008	Gemcitabine + paclitaxel (q3w) n=266	Paclitaxel (q3w) n=263	First-line LR/mBC	Albain K et al. J Clin Oncol 2008; 26: 3950−57.
CALGB 9840	Paclitaxel (weekly) n=350	Paclitaxel (q3w) n=385	mBC, predominantly first-line (19% 2nd-line)	Seidman A et al. J Clin Oncol 2008; 26: 1642−49.
Jones 2005	Docetaxel n=225	Paclitaxel (q3w) n=224	Locally advanced/mBC, first-line (45%) and 2nd-line (55%)	Jones S et al. J Clin Oncol 2005; 23: 5542−51.

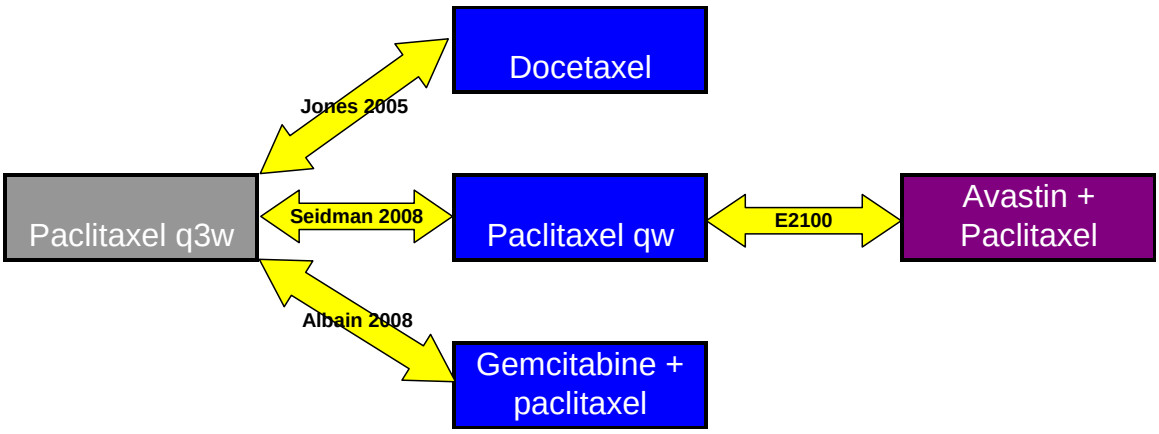
LR: Locally recurrent; mBC: Metastatic breast cancer; q3w: Every 3 weeks.

Table 19 continued. Relevant RCTs – treatment and patient characteristics

Trial	Dosage		Median no. cycles[a]		Age in years Mean (median)		ER (+) (%)		HER2+ (%)		Number (%) of patients with <3 metastatic sites		Previous adjuvant chemo (%)[b]		Previous chemo for metastatic disease (%)	
E2100	B 10 mg/kg* q2w + Pac 90 mg/m^2 qw[† *]	Pac 90 mg/m^2 qw[† *]	B/ Pac 10	Pac 6	B/ Pac 56	Pac 55	B/ Pac 63.0	Pac 60.7	B/ Pac 2.7	Pac 1.7	B/ Pac 71.2	Pac 71.2	B/ Pac 65.3	Pac 65.0	B/ Pac 0	Pac 0
Albain 2008	Gem 1250 mg/m^2 d1, d8, q3w* + Pac 175 mg/m^2 q3w*	Pac 175 mg/m^2 q3w*	GP 6.4	Pac 5.7	GP 53	Pac 53	GP 33.1	Pac 31.9	NR		GP 56.8	Pac 58.6	GP 100	Pac 92.2	GP 0	Pac 0
CALGB 9840	Pac 175 mg/m^2 q3w*	Pac 80 mg/m^2 qw*	NR		25% <50 years q3w	18% <50 years qw	66 q3w	77 qw	NR		NR		NR		28 q3w	9 qw
Jones 2005	D 100 mg/m^2 q3w*	Pac 175 mg/m^2 q3w*	D 6	Pac 4	D 56	Pac 54	D 51.1	Pac 42.0	NR		Median 2		D 51.6	Pac 53.2	D 58.2	Pac 52.7

[†] Weeks 1-3, no Pac treatment week 4 ; * Until disease progression or intolerable toxicity. B: Bevacizumab; D: Docetaxel; Gem: Gemcitabine; GP: Gem + Pac; NR: Not reported; Pac: Paclitaxel; Pl: Placebo; qw: Weekly; q2w: Every 2 weeks; q3w: Every 3 weeks.

Figure 8. Relevant RCTs – Network



6.6.5 Indirect comparison of Avastin + paclitaxel compared to docetaxel monotherapy and compared to gemcitabine in combination with paclitaxel

Because of the lack of direct (head to head) evidence, indirect comparisons have been recommended and used for evaluating the relative efficacy of alternative interventions (McAlister *et al.* 1999). However, the above systematic review would suggest that there are few optimal studies to include in an indirect treatment comparison and therefore the results of such an analysis should be evaluated in this context. The following presents the indirect comparisons with bevacizumab in combination with paclitaxel compared to both docetaxel monotherapy and gemcitabine in combination with paclitaxel for the purpose of supporting the economic analysis described in Section 7.2.

Three RCTs were identified as being most relevant to compare, indirectly, to BEV/PAC based on similar inclusion/exclusion criteria and baseline patients characteristics (Jones *et al.* 2005; Seidman *et al.* 2008; Albain *et al.* 2008); however, as described above, none of these RCTs have all the desired characteristics for inclusion in the network. An indirect comparison via a common comparator was carried out according to the method suggested by Bucher (Bucher *et al.* 1997) and Song (Song *et al.* 2003) to compare alternative therapies in which no head-to-head RCT has been conducted, The selection of relevant studies from the systematic review was extremely limited resulting in inadequate power to test for heterogeneity between indirect comparators. However

based on the similar population, baseline characteristics and exclusion/inclusion criteria it is assumed that heterogeneity would not be significant (McAlister *et al.* 1999; Bucher *et al.* 1997; Song *et al.* 2003).

PFS Hazard Ratios

The hazard ratios are normal on the log scale and the sum of two or independent normally distributed variables also follow a normal distribution with the mean being the sum of the individual study means (LN(HR)) and the pooled variance being the square root of the summed squared study variances (SE(LN(HR)). Variance heterogeneity was not assessed however the variances from the three studies were similar suggesting that any variance heterogeneity would not be significant (Table 19). Jones et al, reported the hazard ratios and associated 95% CIs for overall survival and progression free survival. Seidman et al however reported the progression free HR of 1.43 but did not report the 95% CIs. Seidman did however report the number of progressive events. Thus an estimate of the standard error of the hazard ratio was able to be calculated (Tudur *et al.* 2001). However due to the large number of events reported in this study the SE(LN HR)) is smaller than what was observed in the E2100 study or Jones et al. This difference is due to the small number of censored patients in the Seidman publication (300 events n=350) compared to 170 events (n=354) in the E2100 study in the treatment arms of interest.

Docetaxel

The indirect comparison of docetaxel to bevacizumab + paclitaxel is based on the phase III RCT of docetaxel compared to paclitaxel (Jones 2005). Patients (n=449) were randomly assigned to receive until progressive disease, unacceptable toxicity or withdrawal of consent either docetaxel 100mg/m² or paclitaxel 175 mg/m² on day 1 of 21 day cycles (this represents a limitation as noted above as the standard UK dose is less than docetaxel 100mg/m²). In comparison, patients in study E2100 received 90mg/m² weekly paclitaxel for 3 weeks followed by one week of rest (cycle length of 28 days).

A phase III, RCT comparing response rates with the administration of weekly paclitaxel (80mg/m²) to paclitaxel (175mg/m²) every 3 weeks (cycle length 21 days) for patients with metastatic breast cancer (Seidman *et al.* 2008) was needed to compare BV/PAC from the E2100 study to docetaxel q3w (Jones *et al.* 2005). The derived hazard ratios used to make possible the comparison of BV/PAC to docetaxel are reported in Table 20.

Gemcitabine + Paclitaxel

A randomised phase III multicenter, open-label study of gemcitabine 1,250mg/m² and paclitaxel 175mg/ m² on day 1 versus paclitaxel 175mg/ m² alone administered on day 1 on a 21 day cycle was conducted to gain approval of gemcitabine for treatment of breast cancer (Albain *et al.* 2008). The primary endpoint of this study was overall survival with progression free survival as a secondary endpoint. Hazard ratios and 95% CIs were reported for PFS.

The final scope for this appraisal requested a comparison of bevacizumab + paclitaxel to gemcitabine + paclitaxel. Like the docetaxel comparison, no head-to-head study had been conducted comparing these two regimens. Additionally there is a difference in administration and dose intensity between the gemcitabine + paclitaxel (Albain *et al.* 2008) and the E2100 study. As in the docetaxel indirect comparison described above, the Seidman study (Seidman *et al.* 2008) was required to make the comparison between these two studies possible. The hazard ratios for PFS derived from the indirect treatment comparison are reported in Table 21.

Results and discussion

The PFS hazard ratio for bevacizumab in combination with paclitaxel is estimated to be 0.555 compared to docetaxel monotherapy and 0.464 compared to gemcitabine in combination with paclitaxel. The PFS hazard ratio for paclitaxel weekly compared to docetaxel 3-weekly is 1.147 and the hazard ratio for paclitaxel weekly compared to gemcitabine in combination with paclitaxel 3-weekly is 0.958. Both of these latter comparison were not statistically significantly (the confidence interval included the value

1). As discussed above, due to the limitations of the evidence required to build the indirect comparison, these point estimates should be interpreted with caution.

This method aims to overcome the potential problem of different prognostic characteristics between study participants among trials by preserving randomisation and utilising relative treatment effects. It is validated if the relative efficacy of interventions is consistent across different trials (McAlister *et al*. 1999; Bucher *et al.* 1997; Song *et al.* 2003). A limitation of this approach under these circumstances is the use of three trials required to achieve the indirect comparisons. As observed in the standard errors on the log scale provided in the tables above, this lends greatly to the level of uncertainty in these point estimates. However, as the systematic review has not identified any publications which will allow for use of fewer trials to arrive at the indirect comparison shown below, this limitation can only be discussed but not corrected.

The potential for unknown heterogeneity exists and there is insufficient data to assess heterogeneity as no trials were synthesized, only individually compared with one another. It is therefore more important to consider how comparable the populations in these studies are to one another. One of the key observable differences across trials is the extent of previous treatment both in the adjuvant and metastatic setting.

The results obtained from this analysis regarding the indirect comparison between Pac weekly and Doc and Pac weekly and Gem/Pac have been used to support assumptions in the economic analysis (see Section 7).

Table 20 : Indirect Comparison of bev+pac / pac versus docetaxel monotherapy using Hazard Ratios

Progression Free Survival		LN(HR)	SE(LN(HR))	HR	LCL	UCL	
A	HR(BV/Pac q1w vs Pac q1w)	-0.7256704	0.1155326	**0.484**	**0.386**	**0.607**	Study E2100
B	HR(Pac q3w vs Pac q1w)	0.35767444	0.0779383	1.430	1.23	1.67	Seidman et al. JCO (2008)
C	HR(Pac q3w vs Doc q3w)	0.49469624	0.1063272	1.640	1.33	2.02	Jones et al JCO (2005)
A vsC	H(BV/Pac q1w vs Doc q3w)	-0.5886486	0.175293	**0.555**	0.39	0.78	
B vsC	H(Pac q1w vs Doc q3w)	0.1370218	0.1318327	**1.147**	0.89	1.48	

Table 21 : Indirect Comparison of bev+pac / pac versus gem+pac using Hazard Ratios

Progression Free Survival		LN(HR)	SE(LN(HR))	HR	LCL	UCL	
A	HR(BV/Pac q1w vs Pac q1w)	-0.7256704	0.1155326	**0.484**	**0.386**	**0.607**	Study E2100
B	HR(Pac q3w vs Pac q1w)	0.35767444	0.0779383	1.430	1.23	1.67	Seidman et al. JCO (2008)
C	HR(Gem/Pac q3w vs Pac q3w)	-0.3147107	0.0895146	0.730	0.61	0.87	Albain et al JCO (2008)
A vsC	H(BV/Pac q1w vs GemPac q3w)	-0.7686341	0.1656352	**0.464**	0.34	0.64	
B vsC	H(Pac q1w vs GemPac q3w)	-0.0429637	0.1186897	**0.958**	0.76	1.21	

*Note: Missing SE of the HRs are calculated using the indirect method described in Tudur et al (J.R. Statist Soc. A(2001))

6.7 Safety

Bevacizumab has a side-effect profile distinct from that of cytotoxic chemotherapy, due to its different mode of action. Early studies identified hypertension, bleeding, thrombotic complications and proteinuria as characteristic side-effects of bevacizumab treatment (Hurwitz 2004) and subsequent studies included specific monitoring of these events.

Study E2100

All patients who received any amount of protocol therapy were included in the safety analyses and were analysed based on the treatment received. The safety profile of bevacizumab seen in Study E2100 was consistent with the established safety profile seen in previous bevacizumab studies.

All Grade 3–5 non-hematologic and Grade 4 and 5 hematologic adverse events reported for both treatment arms on the E2100 Toxicity Form were included in the safety analysis. Safety data are based both on events reported on the E2100 Toxicity Form and on those reported to the NCI AdEERS database.

Expedited reporting was conducted through MedWatch (similar to the MHRA 'yellow card' system) for patients in the paclitaxel alone arm. A MedWatch report was required for all unexpected, possibly related Grade 4 and 5 events, including any death that occurred within 30 days of the last dose of treatment and any death that occurred ≥30 days after the last dose of treatment but was at least possibly attributed to paclitaxel.

Expedited reporting was conducted through NCI AdEERS for all bevacizumab-treated patients. For the paclitaxel plus bevacizumab arm, the following protocol-specified adverse events required an NCI AdEERS report:

- Adverse events of any grade that precipitated a hospitalisation of ≥24 hours or that prolonged hospitalisation regardless of attribution, whether expected or unexpected
- Any unexpected Grade ≥2 events that were deemed related to bevacizumab
- All Grade 3 and 4 thrombosis or embolism events, regardless of attribution
- All Grade 2–4 hypersensitivity reactions, regardless of attribution

- All Grade 4 and 5 events (except Grade 4 myelosuppression, unless associated with hospitalisation), including any death that occurred within 30 days of the last dose of treatment and any death that occurred ≥ 30 days after the last dose of treatment but was at least possibly attributed to bevacizumab
- Grade 3 unexpected events that resulted in a hospitalisation of ≥ 24 hours and any Grade 4 unexpected events that occurred ≥ 30 days after the last dose of treatment but was at least possibly attributed to bevacizumab
- Any event that resulted in persistent or significant disability/incapacity, congenital anomaly, or birth defect

Safety reporting procedures were therefore different for the two arms of this study, with more stringent reporting, of lower Grade events, required for the bevacizumab-treated patients.

Overall, no new safety signals were noted with the addition of bevacizumab to first-line paclitaxel therapy for patients with locally recurrent or metastatic breast cancer, relative to events previously identified as associated with bevacizumab. The addition of bevacizumab to paclitaxel resulted in a 20% overall increase in the incidence of Grade 3–5 adverse events, driven mainly by an increase in Grade 3 hypertension and sensory neuropathy. Adverse events previously associated with bevacizumab that also occurred more frequently in patients receiving bevacizumab in this study, included hypertension, proteinuria, arterial thromboembolic (ATE) events, bleeding, congestive heart failure (CHF), and gastro-intestinal (GI) perforation. As in several prior bevacizumab studies, there was no observed increase in the incidence of Grade 3–5 vascular thromboembolic (VTE) events with the addition of bevacizumab to paclitaxel.

There was also a higher incidence of neuropathy, neutropenia, and infection/febrile neutropenia events among patients who received paclitaxel plus bevacizumab. Paclitaxel exposure was significantly greater in patients receiving bevacizumab, which may have accounted for this higher incidence. After adjusting for duration of adverse event reporting, the incidence for Grade 3-5 sensory neuropathy was comparable between treatment arms.

Events with a ≥2% difference in incidence between treatment arms are presented in below.

Table 22. Grade 3-5 Non-Hematologic and Grade 4-5 Hematologic Adverse Events Reported on E2100 Toxicity Form or All Grade 3-5 Events Reported in NCI AdEERS by Highest Grade (≥2% Difference in Incidence between Treatment Arms).

	E2100 Toxicity Form Only		AdEERS and E2100 Toxicity Form
Toxicity Category and Term/ NCI-CTC Grade	PAC (n=348)	PAC/BV (n=363)	PAC/BV (n=363)
Any toxicity			
Any toxicity	176 (50.6%)	257 (70.8%)	258 (71.1%)
Grade 5	7 (2.0%)	11 (3.0%)	15 (4.1%)
Grade 4	32 (9.2%)	44 (12.1%)	49 (13.5%)
Grade 3	137 (39.4%)	202 (55.6%)	194 (53.4%)
Neurology			
Any toxicity	74 (21.3%)	109 (30.0%)	110 (30.3%)
Grade 4	3 (0.9%)	11 (3.0%)	14 (3.9%)
Grade 3	71 (20.4%)	98 (27.0%)	96 (26.4%)
Neuropathy-sensory			
Total	61 (17.5%)	88 (24.2%)	88 (24.2%)
Grade 3	59 (17.0%)	86 (23.7%)	86 (23.7%)
Cerebrovascular ischemia			
Total	0 (0.0%)	7 (1.9%)	9 (2.5%)
Cardiovascular (general)			
Any toxicity	28 (8.0%)	79 (21.8%)	83 (22.9%)
Grade 3	18 (5.2%)	74 (20.4%)	76 (20.9%)
Hypertension			
Total	5 (1.4%)	57 (15.7%)	58 (16.0%)
Grade 3	5 (1.4%)	56 (15.4%)	56 (15.4%)
Pain			
Any toxicity	33 (9.5%)	59 (16.3%)	62 (17.1%)
Grade 3	32 (9.2%)	53 (14.6%)	56 (15.4%)
Bone pain			
Total	6 (1.7%)	13 (3.6%)	14 (3.9%)
Headache			
Total	2 (0.6%)	13 (3.6%)	13 (3.6%)
Grade 3	2 (0.6%)	13 (3.6%)	13 (3.6%)

Table 22. continued.

Toxicity Category and Term/ NCI-CTC Grade	E2100 Toxicity Form Only PAC (n=348)	E2100 Toxicity Form Only PAC/BV (n=363)	AdEERS and E2100 Toxicity Form PAC/BV (n=363)
Gastrointestinal			
Any toxicity	21 (6.0%)	57 (15.7%)	58 (16.0%)
Grade 3	18 (5.2%)	53 (14.6%)	54 (14.9%)
Vomiting			
Total	8 (2.3%)	20 (5.5%)	20 (5.5%)
Grade 3	8 (2.3%)	20 (5.5%)	20 (5.5%)
Diarrhea			
Total	5 (1.4%)	17 (4.7%)	17 (4.7%)
Grade 3	5 (1.4%)	17 (4.7%)	17 (4.7%)
Nausea			
Total	5 (1.4%)	15 (4.1%)	15 (4.1%)
Grade 3	5 (1.4%)	15 (4.1%)	15 (4.1%)
Dehydration			
Total	3 (0.9%)	12 (3.3%)	12 (3.3%)
Grade 3	3 (0.9%)	12 (3.3%)	12 (3.3%)
Infection/febrile neutropenia			
Any toxicity	20 (5.7%)	50 (13.8%)	52 (14.3%)
Grade 3	19 (5.5%)	47 (12.9%)	48 (13.2%)
Infection w/o neutropenia			
Total	16 (4.6%)	32 (8.8%)	33 (9.1%)
Grade 3	16 (4.6%)	31 (8.5%)	32 (8.8%)
Infection w/ unknown ANC			
Total	1 (0.3%)	10 (2.8%)	11 (3.0%)
Grade 3	1 (0.3%)	10 (2.8%)	11 (3.0%)
Constitutional symptoms			
Any toxicity	23 (6.6%)	47 (12.9%)	52 (14.3%)
Grade 3	17 (4.9%)	42 (11.6%)	42 (11.6%)

Table 22. continued.

Toxicity Category and Term/ NCI-CTC Grade	E2100 Toxicity Form Only PAC (n=348)	E2100 Toxicity Form Only PAC/BV (n=363)	AdEERS and E2100 Toxicity Form PAC/BV (n=363)
Fatigue			
Total	18 (5.2%)	39 (10.7%)	39 (10.7%)
Grade 3	17 (4.9%)	38 (10.5%)	38 (10.5%)
Pulmonary			
Any toxicity	13 (3.7%)	20 (5.5%)	21 (5.8%)
Grade 3	13 (3.7%)	20 (5.5%)	21 (5.8%)
Dyspnea			
Grade 3	9 (2.6%)	16 (4.4%)	17 (4.7%)
Metabolic/laboratory			
Any toxicity	15 (4.3%)	22 (6.1%)	23 (6.3%)
Grade 3	10 (2.9%)	19 (5.2%)	20 (5.5%)
Blood/bone marrow			
Any toxicity	13 (3.7%)	22 (6.1%)	22 (6.1%)
Grade 4	13 (3.7%)	22 (6.1%)	22 (6.1%)
Neutrophils			
Total	11 (3.2%)	21 (5.8%)	21 (5.8%)
Grade 4	11 (3.2%)	21 (5.8%)	21 (5.8%)
Dermatology/skin			
Any toxicity	6 (1.7%)	15 (4.1%)	19 (5.2%)
Grade 3	6 (1.7%)	15 (4.1%)	18 (5.0%)
Rash/desquamation			
Total	1 (0.3%)	7 (1.9%)	9 (2.5%)
Grade 3	1 (0.3%)	7 (1.9%)	9 (2.5%)
Renal/genitourinary			
Any toxicity	2 (0.6%)	16 (4.4%)	17 (4.7%)
Grade 3	1 (0.3%)	13 (3.6%)	12 (3.3%)
Proteinuria			
Total	0 (0.0%)	10 (2.8%)	11 (3.0%)

Grade 3 and 4 adverse events that were increased by ≥5% in patients treated with paclitaxel plus bevacizumab compared with those treated with paclitaxel alone were sensory neuropathy (24.2% vs 17.5%), hypertension (16.0% vs 1.4%), and fatigue (10.7% vs 5.2%). Other categories of events, when combined, also showed increases of ≥5%, although no individual toxicity within these categories was increased to the same

degree. These include the categories of pain events (17.1% vs 9.5%), GI toxicity (16.0% vs 6.0%), and infection and febrile neutropenia (14.3% vs 5.7%), respectively.

Adverse events of special interest based on safety results from this and other bevacizumab trials included hypertension, proteinuria, arterial and venous thromboembolic events, bleeding, CHF, GI perforation, sensory and motor neuropathy, and neutropenia/infection. The incidence of adverse events of special interest was as follows:

Grade 3–5 hypertension, 16.0% (Grade 5, 0%)
Grade 3–5 proteinuria, 3.0% (Grade 5, 0%)
Grade 3–5 ATE events, 3.6% (Grade 5, 0.6%)
Grade 3–5 VTE events, 3.0% (Grade 5, 0%)
Grade 3–5 bleeding events, 2.2% (Grade 5, 0%)
Grade 3–5 CHF, 2.2% (Grade 5, 0%)
GI perforation events, 0.6% (Grade 5, 0.6%)
Grade 3–5 neuropathy events, 25.3% (Grade 5, 0%)
Neutropenia/infection, 17.4% (Grade 5, 0.3%)

Deaths

The causes of death were similar between the two treatment arms, with the vast majority of deaths considered by the investigator to be due to metastatic breast cancer for patients in both treatment arms. There was no increase and possibly even a slight reduction in deaths due to reasons other than metastatic breast cancer in patients who received paclitaxel bevacizumab. Only one patient died as a result of protocol therapy, and that patient received paclitaxel alone. Consistent with all reported deaths, the majority of deaths within 30 days of the last dose of protocol therapy in both treatment arms were considered by the investigator to be the result of metastatic breast cancer.

The E2100 safety database, collected from 711 patients is augmented with safety data gathered in the non-randomised Study MO19391, ATHENA. This study recruited 2,251

patients with metastatic breast cancer, treated with bevacizumab, for the primary purpose of assessing bevacizumab safety (See below).

6.8 Non-RCT evidence

6.8.1 Summary of methodology of relevant non-RCTs

Study MO19391, ATHENA: An Open-label Study to Evaluate the Safety and Effect on Disease Progression and Overall Survival of Avastin Plus Taxane-based Chemotherapy in Patients With Locally Recurrent or Metastatic Breast Cancer.

The primary objective of this open-label, phase IIIB or IV study was to assess the safety profile of bevacizumab when given in combination with taxane, as monotherapy or in combination, in patients who had not received prior chemotherapy for locally recurrent or metastatic breast cancer. This ongoing study is being sponsored and the data owned by Hoffmann-La Roche.

This was a multicentre, non-randomised, single-arm, open-label study evaluating the safety and efficacy of bevacizumab when combined with a taxane, as first-line treatment of patients with HER2-negative locally recurrent or metastatic breast cancer. HER2-positive patients were eligible if their disease had progressed after previous trastuzumab treatment in the adjuvant setting and they were no longer eligible for specific anti-HER2-positive treatment.

Patients received bevacizumab 10mg/kg every 2 weeks, or 15mg/kg every 3 weeks, according to chemotherapy regimen schedule. The choice of taxane, its dose, use of taxane monotherapy or in combination with another chemotherapy, as well as the schema of its administration was at the discretion of the treating physician. If taxanes were contraindicated, alternative chemotherapy (with the exception of anthracyclines) was allowed, given in combination with bevacizumab. Patients received bevacizumab and chemotherapy until disease progression, as assessed by the investigator, or

unacceptable toxicity. However if chemotherapy was stopped before progressive disease, the patient could continue to receive bevacizumab and vice versa.

Tumour assessments were performed by the investigator at baseline and at the final visit. Tumour assessments during protocol therapy were performed according to standard clinical practice. After the final visit patients were followed every 3 months for evaluation of treatment response and survival status. Adverse events were monitored and recorded on an ongoing basis during treatment and any serious adverse events (SAEs) considered related to bevacizumab will be reported for the duration of the study. The end of the study was defined as 2 years after the date the last patient was enrolled, or the death of all patients.

Patient numbers

The protocol specified the enrolment of a minimum of 2000 patients who had not previously received chemotherapy for their locally recurrent or metastatic disease and were candidates for taxane-based chemotherapy (either as monotherapy or in combination). This large number of patients was enrolled in order to evaluate the occurrence of rare adverse events, which might be seen in fewer than 1% of patients.

Outcomes

The primary objective was to assess the safety profile of bevacizumab when combined with taxane, as monotherapy or in combination, as first-line treatment of patients with locally recurrent or metastatic breast cancer. Secondary objectives were to assess efficacy, as measured by time to disease progression and overall survival and to assess the safety of bevacizumab in patients who developed CNS metastases during and for 6 months following the treatment period.

The primary endpoint of safety included the incidence of SAEs related to bevacizumab and the incidence of specific adverse events (serious and non-serious), including hypertension, proteinuria, arterial and venous thromboembolism, congestive heart failure, CNS bleeding, other haemorrhages, wound-healing complications and gastrointestinal perforations.

The secondary endpoint of duration of survival was defined as the time from the first dose of bevacizumab to death from any cause. Patients for whom no death is captured on the clinical database will be censored at the last date they were known to be alive. Time to disease progression was defined as the time from first dose of bevacizumab to investigator-assessed disease progression by RECIST criteria, on X-rays or CT- or MRI scans. Patients who have not progressed at the time of study completion (including patients who have died before progressive disease) or who are lost to follow-up will be censored at the last bevacizumab administration date.

The incidence of CNS bleeding in patients who developed CNS metastases during the study period and without CT/MRI imaging techniques of the brain performed at baseline will be assessed as a further secondary endpoint. For patients who are taken off study due to CNS metastases or CNS bleeding (grade ≥ 2), the date and type of scan confirming the diagnosis were recorded.

Statistical analysis and definition of study groups

The ITT population included all patients with at least one valid post-baseline assessment. The analysis of demographics, baseline characteristics, safety and the secondary endpoints were based on the ITT population. An analysis based on the partner chemotherapy groups was performed on the ITT population. In addition, patients with ECOG performance status of 2 were analysed separately. Cohort populations relating to CT/MRI scans of the brain performed at baseline were analysed.

All adverse events, SAEs and specific adverse events of interest were summarized by incidence rates. For SAEs and specific adverse events, 95% Pearson Clopper confidence intervals will be presented. Specific adverse events include neutropenia, hypertension, proteinuria, arterial and venous thromboembolic events, congestive heart failure, CNS bleeding, other haemorrhages, wound-healing complications, gastrointestinal perforation, fistulas and RPLS.

Kaplan-Meier methodology was used to estimate overall survival and time to disease progression.

6.8.2 Critical appraisal of relevant non-RCTs

The primary purpose of this large open-label study was to evaluate the safety of bevacizumab in a very large population of first-line metastatic breast cancer patients in routine clinical practice. The large sample size was adequately justified, as providing sufficient data to evaluate the incidence of adverse events occurring with a frequency of less than 1%. The follow-up of patients, with continued reporting of adverse events until death was adequate for this purpose.

The study was conducted in many countries worldwide, with more than 60 patients entered in the UK. The study protocol allowed the enrolment of a slightly wider group of first-line metastatic patients than in E2100, as patients not suitable for taxane therapy were included. This reflects the more routine clinical practice seen in the UK, where not all patients are eligible for taxane therapy.

The dosing of bevacizumab in this study was according to the recommendations in the Summary of Product Characteristics. The dosing of the background chemotherapy, which in most patients was taxane-based, was according to the standard of care in the participating institutions, including those in the UK.

The study analysis was conducted on an intention to treat basis.

6.8.3 Results of the relevant non- RCTs

Database cut-off for this report (Smith *et al.* 2010) was 3 August 2009. Between 22 September 2006 and 26 March 2009, 2,251 patients were recruited in 37 countries. Median follow-up was 12.7 months (range 0.03–27.3). All but 12 patients (0.5%) were female. Demographic data are shown in Table 23. Of the 1,794 patients initially presenting with early breast cancer, 1,696 (94.5%) had received adjuvant or neoadjuvant therapy, including chemotherapy in 88.4%. Endocrine therapy had been given for LR/mBC in 23.6% of patients.

Table 23. Study MO19391, ATHENA Patient Demographics and Baseline Characteristics

	Safety population (n = 2,251)
Median age, years (range)	53 (21–93)
ECOG performance status, n (%)*	
0	1,306 (58.0)
1	819 (36.4)
2	124 (5.5)
3	1 (<0.1)
Disease-free interval, n (%)*	
≤ 24 months	662 (29.4)
> 24 months	1,215 (54.0)
Not applicable	373 (16.6)
Number of metastatic lesions, n (%)	
≤ 3	643 (28.6)
> 3	1,440 (64.0)
Missing	168 (7.5)
Metastatic sites	
Bone	1,101 (48.9)
Liver	812 (36.1)
Lung	808 (35.9)
Brain	2 (0.1)
Steroid hormone receptor status, n (%)†	
Estrogen receptor positive	1,471 (66.1)
Progesterone receptor positive	1,183 (53.1)
HER2 status positive†	62 (2.8)
History of cardiovascular comorbidity	658 (29.2)
Ongoing hypertension at study start	490 (21.8)

*Missing in one patient.
†n=2,227.
ECOG, Eastern Cooperative Oncology Group.

Treatment exposure

Bevacizumab was typically combined with single-agent paclitaxel (35%) or single-agent docetaxel (33%). The paclitaxel administration schedule was weekly in 17%, 3-weekly in 13%, and other in 6%. A further 10% of patients received taxane-based combination regimens, most commonly with carboplatin or gemcitabine. The non-taxane monotherapies most frequently combined with bevacizumab were capecitabine (5%) and vinorelbine (3%).

The median duration of treatment was 6.2 months for bevacizumab (range 0.0–27.9) and 4.2 months for chemotherapy (range 0.0–29.5). Among 1,316 patients whose

disease had progressed at the time of data cut-off, 479 (36%) had continued bevacizumab and chemotherapy until disease progression and a further 525 patients (40%) had received single-agent bevacizumab until disease progression after discontinuing chemotherapy. The median duration of single-agent bevacizumab in the latter group was 4.1 months (95% CI 3.7–4.4).

Primary outcome; safety

At the time of data cut-off, 16% of patients had not had their final visit (often because patients were still receiving therapy); 18% had received bevacizumab for > 1 year. SAEs (all grades, irrespective of relationship to treatment) were reported in 655 patients (29%) (Table 24). The most frequent SAEs were febrile neutropenia (5.1%), neutropenia (3.6%), and pyrexia (1.5%). Table 25 summarises pre-defined grade ≥ 3 AEs of special interest. Bevacizumab was discontinued permanently in 18.9% of patients because of AEs, most commonly hypertension (1.8%), fatigue (1.2%), and proteinuria (1.0%).

CNS metastases were documented in 205 patients (9.1%) during the study. Four of these patients (2.0% of 205; 0.2% of the entire study population) experienced CNS bleeding during the study or survival follow-up. The median interval between first treatment administration and diagnosis of CNS metastases was 10.5 months (range 0.0 –27.3).

To evaluate whether bevacizumab exposure increases the risk of soft tissue and hemorrhagic toxicities following surgery, post-surgical bleeding events and wound-healing complications were reviewed in the 496 patients who underwent surgery. There were no grade ≥4 bleeding events; grade 3 bleeding was reported in three (1.5%) of 194 patients who received major surgery and two (0.7%) of 302 patients who underwent minor surgery. Grade 3 and 4 wound-healing complications occurred in 2.6% and 2.0%, respectively (no grade 5).

Table 24.Study MO19391, ATHENA Serious adverse events (all grades, preferred term) reported by ≥ 10 patients, regardless of relationship to treatment

Serious adverse event, no. of patients (%)	Safety population, n = 2,251
Patients with ≥ 1 event	655 (29.1)
Febrile neutropenia	114 (5.1)
Neutropenia	81 (3.6)
Pyrexia	34 (1.5)
Dyspnea	23 (1.0)
Pulmonary embolism	23 (1.0)
Hypertension	19 (0.8)
Vomiting	18 (0.8)
Pneumonia	18 (0.8)
Deep vein thrombosis	14 (0.6)
Sepsis	14 (0.6)
Febrile bone marrow aplasia	13 (0.6)
Infection	13 (0.6)
Wound-healing complications	12 (0.5)
Central line infection	12 (0.5)
Diarrhea	11 (0.5)
Congestive heart failure	11 (0.5)
General physical health deterioration	10 (0.4)

Table 25. Adverse Events of Special Interest[a] (Grade ≥ 3) Reported in ≥ 5 Patients, Regardless of Relationship to Treatment

	Safety population, n = 2,251		
Adverse event, no. of patients (%)	Grade 3	Grade 4	Grade 5
Patients with ≥ 1 event	211 (9.4)	38 (1.7)	16 (0.7)
Hypertension	95 (4.2)	4 (0.2)	0.0
Proteinuria	34 (1.5)	5 (0.2)	0.0
Arterial/venous thromboembolism	51 (2.3)	17 (0.8)	6 (0.3)
Pulmonary embolism	9 (0.4)	12 (0.5)	3 (0.1)
Deep vein thrombosis	14 (0.6)	0.0	0.0
Wound-healing complications	8 (0.4)	6 (0.3)	0.0
Hemorrhage	24 (1.1)	5 (0.2)	3 (0.1)
Epistaxis	7 (0.3)	1 (<0.1)	0.0
Gastrointestinal perforation	2 (0.1)	1 (<0.1)	3 (0.1)
Congestive heart failure	6 (0.3)	1 (<0.1)	3 (0.1)
Central nervous system bleeding	0.0	0.0	1 (<0.1)

[a]Reported in previous clinical trials of bevacizumab

Secondary outcomes; efficacy

At the time of data cut-off, disease had progressed in 58% of patients. The median TTP was 9.5 months (95% confidence interval [CI] 9.1–9.9) and the overall RR (best

response) was 52% in the intent-to-treat (ITT) population. A further 33% achieved stable disease. At data cut-off, 1,622 patients (72%) were still alive and survival follow-up is ongoing. The most common cause of death was breast cancer (24%). The remaining deaths were attributed to concurrent illness (0.5%), outcome of AE (0.4%), chemotherapy (0.3%), bevacizumab (0.2%), or other/unknown cause (2.2%).

In the group of 205 patients who developed CNS metastases during the study, median TTP was 7.1 months (95% CI 6.7–7.8) and median OS was 14.6 months (95% CI 13.1–17.0).

Subpopulation Analyses

To examine whether the efficacy and safety of bevacizumab varied according to chemotherapy partner, a planned subpopulation analysis was performed. The majority of patients (78%) received bevacizumab with a taxane (alone or with another chemotherapy). Chemotherapy was switched before evidence of progressive disease in 12% of patients. The baseline characteristics of the seven subpopulations were generally balanced. There were no clear differences in bevacizumab-associated AEs between chemotherapy cohorts, except for a higher incidence of grade ≥ 3 AEs in patients who switched chemotherapy (Table 26). Median TTP was longer with taxane-based than non-taxane-containing bevacizumab regimens (Table 26) and was longest in patients who switched chemotherapy.

Table 26. Study MO19391, ATHENA Safety and Efficacy: Subanalysis According to Chemotherapy Partner

	Monotherapy*				Combination		Switched chemotherapy before progression (n = 276)
	Paclitaxel (n = 777)	Docetaxel (n = 742)	Cape-citabine (n = 102)	Vinorelbine (n = 57)	Taxane combination (n = 235)	Non-taxane combination (n = 52)	
Grade ≥ 3 AEs, %	47.5	60.4	45.1	57.9	51.5	46.2	65.9
Serious AEs any grade, %	24.3	35.0	21.6	36.8	22.6	25.0	34.1
Grade ≥ 3 AEs of special interest, %							
Hypertension	4.6	4.4	5.9	3.5	3.0	9.6	3.6
Proteinuria	2.7	1.2	1.0	3.5	1.3	1.9	0.7
Arterial/venous thromboembolism	3.0	3.1	4.9	3.5	2.6	3.8	4.3
Wound-healing complications	0.5	1.1	0.0	0.0	0.4	0.0	0.4
Hemorrhage	1.4	2.3	1.0	0.0	0.9	0.0	0.0
Epistaxis	0.4	0.5	0.0	0.0	0.4	0.0	0.0
Gastrointestinal perforation	0.4	0.3	0.0	0/0	0.4	0.0	0.0
Congestive heart failure	0.4	0.3	0.0	1.8	0.0	1.9	1.1
Central nervous system bleeding	0.0	0.0	0.0	0.0	0.4	0.0	0.0
Overall response rate, %†	49.3	58.6	36.3	28.1	50.2	42.3	56.9
Complete response	9.1	6.2	2.0	8.8	12.8	5.8	8.0
Partial response	40.2	52.4	34.3	19.3	37.4	36.5	48.9
Stable disease, %	33.2	29.1	42.2	43.9	37.4	28.8	34.1
Time to progression							
No. of events, %	475 (61.1)	402 (54.3)	82 (80.4)	38 (66.7)	119 (50.6)	31 (59.6)	162 (58.7)
Median, months (95% CI)	9.8 (9.1–10.5)	8.8 (8.4–9.4)	7.0 (5.8–8.6)	8.4 (5.7–12.0)	10.9 (9.8–12.2)	6.8 (5.8–12.0)	11.3 (10.2–13.5)
Alive at data cut-off, %	71	77	60	51	75	58	72

*Ten patients who received bevacizumab in combination with single agents other than taxane, capecitabine, or vinorelbine were excluded from the analysis because the small number in this subgroup precluded meaningful interpretation.
†Patients with non-evaluable disease or no tumor assessment counted as non-responders.
AEs, adverse events; CI, confidence interval.

In the group of 205 patients who developed CNS metastases during the study, median TTP was 7.1 months (95% CI 6.7 to 7.8) and median OS was 14.6 months (95% CI 13.1 to 17.0).

These data, in a very large group of patients, confirm the efficacy of bevacizumab plus paclitaxel seen in the phase III study reported above. They demonstrate that in a less stringently selected population, treated according to the clinician's routine practice, bevacizumab plus paclitaxel gave an objective response rate of 49.3% and a median time to progression of 9.8 months. These results exceed the response rates and median times to progression previously seen in the majority of phase III RCTs of first-line cytotoxic chemotherapy in metastatic breast cancer.

Overview of safety, studies E2100 and MO19391, ATHENA

The ATHENA study confirms, in a very large pragmatically-treated population, the safety profile of bevacizumab in first-line metastatic breast cancer. Although safety reporting was as strictly adhered to in ATHENA as in E2100, the level of serious adverse events was considerably lower in the ATHENA study. The latter study reflected more closely the use of bevacizumab and chemotherapy in the routine clinical population of metastatic breast cancer patients. The reported levels of Grade 3-5 hypertension (4.4%), proteinuria (1.7%), arterio and venous thromboembolism (3.4%) and coronary heart failure (0.5%) in ATHENA were all considerably lower than the levels reported in E2100. This may reflect the growing experience of clinicians in patient management with bevacizumab, such that many adverse events can be avoided.

The most common adverse events associated with bevacizumab therapy, hypertension and proteinurea, are those which might be anticipated from the mechanism of action of the drug. Because VEGF activity is associated with vasodilatation, neutralisation of VEGF by bevacizumab is likely to result in vasoconstriction, which in turn may lead to hypertension in some patients. The proteinurea seen in some patients (more commonly in those with pre-exisiting hypertension) is probably also related to this mechanism. In the clinical studies, the vast majority of these adverse effects resolved, either with interruption of bevacizumab therapy or by institution of simple therapeutic measures such as oral anti-hypertensive medication.

It is clear from analysis of the safety data that bevacizumab is not associated with the commonly recognised side-effects of cytotoxic anti-cancer therapies. Although there was some increase in sensory neuropathy and fatigue in the bevacizumab plus

paclitaxel arm of the E2100, this study might be largely due to the greater exposure to paclitaxel in this arm of the study.

6.9 Interpretation of clinical evidence

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

The phase III RCT E2100 demonstrates the efficacy of bevacizumab in combination with weekly paclitaxel, in a population of predominantly HER2-negative patients with previously untreated metastatic breast cancer. This study therefore addresses the intervention and population referred to in the decision problem. The study is also in accordance with the marketing authorisation for bevacizumab in advanced breast cancer.

The population in the large non-randomised ATHENA study more closely reflects the potentially eligible population in the UK, than does the E2100 study population. The outcomes, in terms of efficacy and safety of bevacizumab plus taxane therapy, seen in ATHENA closely mirror those described in the RCT.

The primary outcome of progression-free survival in the E2100 study is of very considerable importance to patients in routine practice. It has been shown that recurrence of their disease, at progression, is the most feared event for cancer survivors (Hersbach *et al.* 2004). The secondary outcome of objective disease response is also very important to patients, as shrinkage of their lesions correlates with an improved QoL and patient well-being (Baum *et al.* 1980, Coates *et al.* 1987).

In addition, the secondary outcome of overall survival (OS) is the outcome of greatest relevance to the treatment of all cancer patients. The significant benefit in OS seen at 1 year in the E2100 study is of very great importance to the treatment of metastatic breast cancer patients with a poor prognosis.

The QoL data from E2100 show that the outcomes measured in these studies gave a relevant and meaningful benefit to the patients.

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

Docetaxel is the first-line chemotherapy recommended in NICE Clinical Guideline 81 for patients with metastatic breast cancer who are unable to receive anthracycline therapy. Data from the RCT in this submission refer to the combination of bevacizumab with weekly paclitaxel, which as noted in the NICE Guideline 81, should, under certain circumstances, be considered for first-line therapy.

NICE Guideline 81 states that combination therapy should be considered "for patients for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity" (NICE CG81 2009). This submission provides evidence for a combination therapy (bevacizumab) which when added to a recommended first-line taxane, provides a very significant increase in response rate and a very significant reduction in the risk of progression. This improvement in outcomes is achieved without a large increase in toxicity likely to reduce patients' QoL.

The patients recruited to the RCT were representative of many of the first-line metastatic breast cancer population seen in NHS clinics. However, the large non-randomised ATHENA study recruited a slightly wider patient group, representing the full spectrum of patients eligible for first-line chemotherapy for metastatic breast cancer. The efficacy outcome for patients given paclitaxel in the ATHENA study were close to those in E2100, demonstrating that the results shown are generally representative of those that will be achieved with bevacizumab plus paclitaxel therapy for metastatic breast cancer in routine clinical practice.

The significant benefit in OS seen at 1 year in the E2100 study occurred at a time when crossover was minimal and may show the true benefit of bevacizumab for OS in the population as a whole. The subgroup data demonstrate that particular subgroups of patients who are associated with high-risk disease may achieve very significant clinical benefit with bevacizumab, including a significant increase in their OS.

The safety data from the large ATHENA study back-up those seen in E2100 and show that bevacizumab does not add significantly to 'chemotherapy' type toxicities. The ATHENA study also demonstrated that specific toxities associated with bevacizumab, such as hypertension and proteinurea occurred at a rather lower level in this non-RCT study, which was more representative of routine clinical practice than the phase III RCT.

All the evidence from the studies shown in this submission reflect use in an appropriate therapy setting at the recommended dose from the Avastin SPC.

7 Cost-effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

The search strategy was designed to retrieve all cost-effectiveness publications and economic evaluations relating to bevacizumab in the first-line treatment of metastatic breast cancer from a UK perspective. Search strategies did not include search terms or filters that would limit results to specific publication types or study design. In addition to broad medical databases (EMBASE, Medline, Medline In-Process), health economic databases were searched (HEED, NHS EED).

The full search strategy is detailed in appendix 3, section 10.3. An overview of the search is provided below.

EMBASE/Medline/Medline In-Process

Searches used index and text words which included bevacizumab and breast cancer as major descriptors, and economic evaluation/cost-effectiveness terms as descriptors. The search was not restricted according to publication type or study design. Where possible the search was restricted to metastatic or advanced breast cancer. There were no restrictions by language or date. The searches for EMBASE, Medline and Medline In-Process were conducted together using Dialog Datastar, and the results electronically combined.

HEED

The HEED database was searched using the terms *bevacizumab* and *breast cancer* as keywords, and terms relating to economic evaluation/cost-effectiveness as the type of economic evaluation. There were no restrictions by article type, language or date.

NHS EED

The NHS EED database was searched using the terms *bevacizumab*, *breast* and *economic*. There were no restrictions by article type, language or date.

Exclusion criteria

Duplicate records identified in more than one of the searches above were manually dropped. The following exclusion criteria were applied to the remaining records:

- Studies that were not an economic evaluation/did not evaluate cost-effectiveness as an outcome measure were excluded
- Studies that were not concerned with bevacizumab in the first-line treatment of metastatic breast cancer, and are therefore not relevant to the decision problem were excluded
- Analyses that were only performed from a non-UK perspective were excluded

7.1.2 Description of identified studies

No publications evaluating the cost-effectiveness, or examining the health economics, of bevacizumab in the first-line treatment of metastatic breast cancer from a UK perspective were identified.

The following publications were identified by the search strategy, but excluded based on the criteria outlined in section 6.1.1. Details of the records identified and rationale for their exclusion are provided in Table 27.

Table 27. Studies identified by cost-effectiveness search.

	Database	Reference	Reason for exclusion
1.	EMYY	Dedes K et al. Bevacizumab in combination with paclitaxel for HER-2 negative metastatic breast cancer: An economic evaluation. Eur J Cancer, 2009; 45: 1397-406.	Evaluation performed from a non-UK perspective – Swiss study
2.	MEIP	Moreno A, Perez E. Anthracycline- and/or taxane-resistant breast cancer: results of a literature review to determine the clinical challenges and current treatment trends. Clin Ther 2009; 31: 1619-40.	Not an economic evaluation – review article
3.	EMYY	Drucker A et al. The cost burden of trastuzumab and bevacizumab therapy for solid tumours in Canada. Curr Oncol 2008; 15: 21-27.	Evaluation performed from a non-UK perspective – Canadian study
4.	MEYY	Fumoleau P et al. Angiogenesis targeting in breast cancer. Bull Cancer 2007; 94 (Suppl): F199-206.	Not an economic evaluation – review article
5.	MEIP	Jansen R, Gouws C. Clinical, legal and ethical implications of the intra-ocular (off-label) use of bevacizumab (avastin)--a South African perspective. S Afr Med J 2009; 99: 446-49.	Not relevant disease – ocular use of bevacizumab
6.	HEED	Kruse G et al. Analysis of costs associated with administration of intravenous single-drug therapies in metastatic breast cancer in a U.S. population. J Managed Care Pharm 2008; 14: 844-57.	Evaluation performed from a non-UK perspective – US study

7.2 De novo economic evaluation(s)

The manufacturer economic model is described in detail below. The focus of the evaluation is on the intervention of bevacizumab in combination with paclitaxel. The cost-effectiveness of bevacizumab in combination with docetaxel is discussed in section 7.3.

7.2.1 Technology

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

The technology (bevacizumab) is assumed to be used as indicated in its UK Summary of Product Characteristics (SPC). Bevacizumab is administered by infusion in combination with paclitaxel until disease progression or unacceptable toxicity. Taxanes are also administered by infusion. The cycle length of bevacizumab in combination with paclitaxel is 28 days. Paclitaxel monotherapy is also assumed to have a 28 day cycle length. The cycle length of comparators docetaxel monotherapy and gemcitabine in combination with paclitaxel is 21 days. The assumed doses for each drug are described in the table below.

Table 28: Drug dose and frequency included within the economic model

Drug	Dose	Dose Frequency	Cycle length	Reference
bevacizumab In combination with paclitaxel	10 mg/kg 90 mg/m^2	Day 1 and 15 Day 1, 8, and 15	28 days	E2100 trial
paclitaxel monotherapy	90 mg/m^2	Day 1, 8, and 15	28 days	E2100 trial
docetaxel monotherapy	75 mg/m^2	Day 1	21 days	docetaxel SPC with dose reduction assumption aligning to UK clinical practice
gemcitabine In combination with paclitaxel	1250 mg/m² 175mg/m²	Day 1 and 8 Day 1	21 days	gemcitabine SPC

The doses listed in this table for bevacizumab and paclitaxel were taken from the E2100 phase III randomised control trial. Paclitaxel in this trial was administered weekly (with a break during week 4) over a 28 day cycle at a dose of 90 mg/m^2. This differs from the licence for paclitaxel monotherapy in metastatic breast cancer which recommends a dose of 175mg/m² every 3 weeks. However, recent studies (Seidman

2008; Sparano 2008) have indicated that weekly paclitaxel is more effective than 3-weekly paclitaxel administration and the E2100 trial used this more effective administration regimen. The good tolerability, plus the high level of efficacy demonstrated for weekly paclitaxel in both early and metastatic breast cancer, means that weekly paclitaxel is becoming a common treatment of choice for metastatic patients in the UK who may be unable to tolerate the more toxic 3-weekly docetaxel regimen.

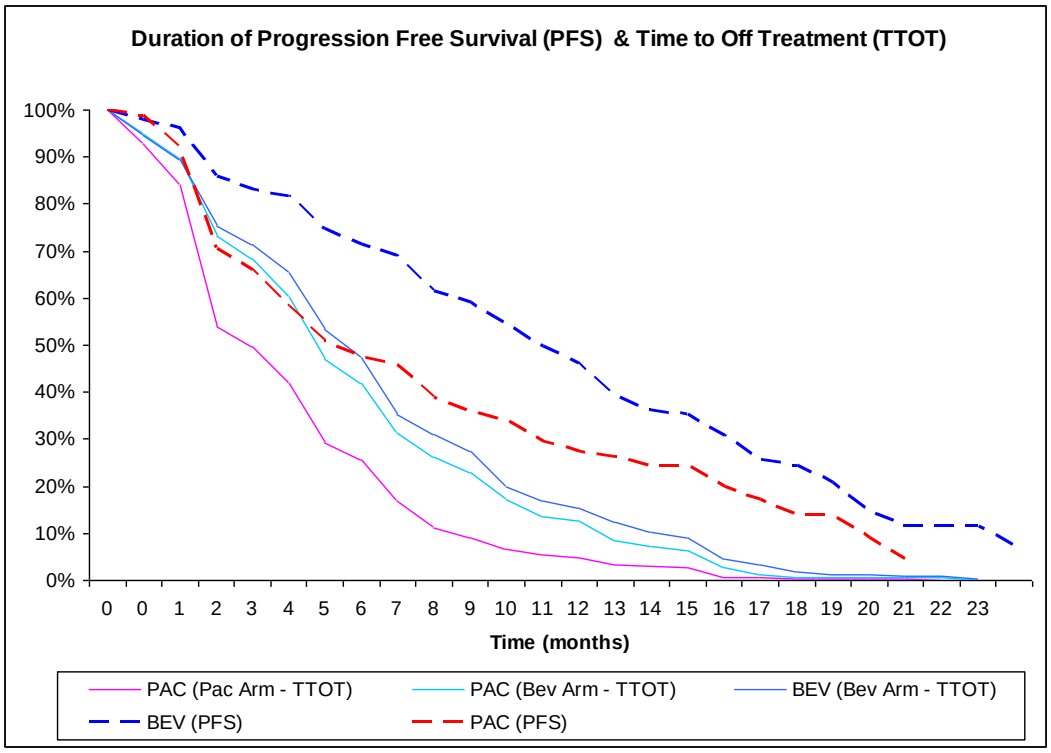
According to the licensed indication for gemcitabine in breast cancer, gemcitabine 1250 mg/m² on days 1 and 8 should be given in combination with paclitaxel 175 mg/m² on day 1 of each 3-week cycle (Gemzar Summary of Product Characteristics) which is in line with the published gemcitabine phase III RCT (Albain 2008). This complicates the comparison of bevacizumab + paclitaxel with gemcitabine + paclitaxel as the RCT data for these two therapies have been generated with different paclitaxel administration regimens. Within this indirect comparison, gemcitabine is at a disadvantage as it is paired with a less effective paclitaxel administration regimen.

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

The base case, bevacizumab + paclitaxel (Bev-Pac) vs paclitaxel (Pac) as defined in the E2100 study protocol assumes that all patients in PFS will receive the recommended course of treatment until unacceptable toxicity, progressive disease or loss to follow up. In practice, as observed in the study, patients will experience dose interruptions or delays and not all patients will be able to tolerate treatment until disease progression. This can be observed in

Figure 9. Dosing was modelled in a similar manner as efficacy (progression free survival) using Kaplan-Meier methods and parametric extrapolation (see Section 7.2.6.9) based upon the dosing curves from the trial.

Figure 9. Time to progression and time to off treatment E2100



To model actual and projected dose observed in the clinical trial by means of parametric extrapolation, it was necessary to develop an algorithm to either censor patients or to code patients as having had an event where “an event” was defined as:

- Having not completed the protocol therapy due to disease progression,
- Dying due to the disease,
- Having been taken off drug prior to disease progression due to unacceptable toxicities, or
- Refusing further treatment whilst not yet experiencing disease progression.

Patients were censored if:

- they were still considered progression free and on the protocol specified study drug at the time of the data cutoff (21 OCT 2006), or
- they died for other than disease related reasons.

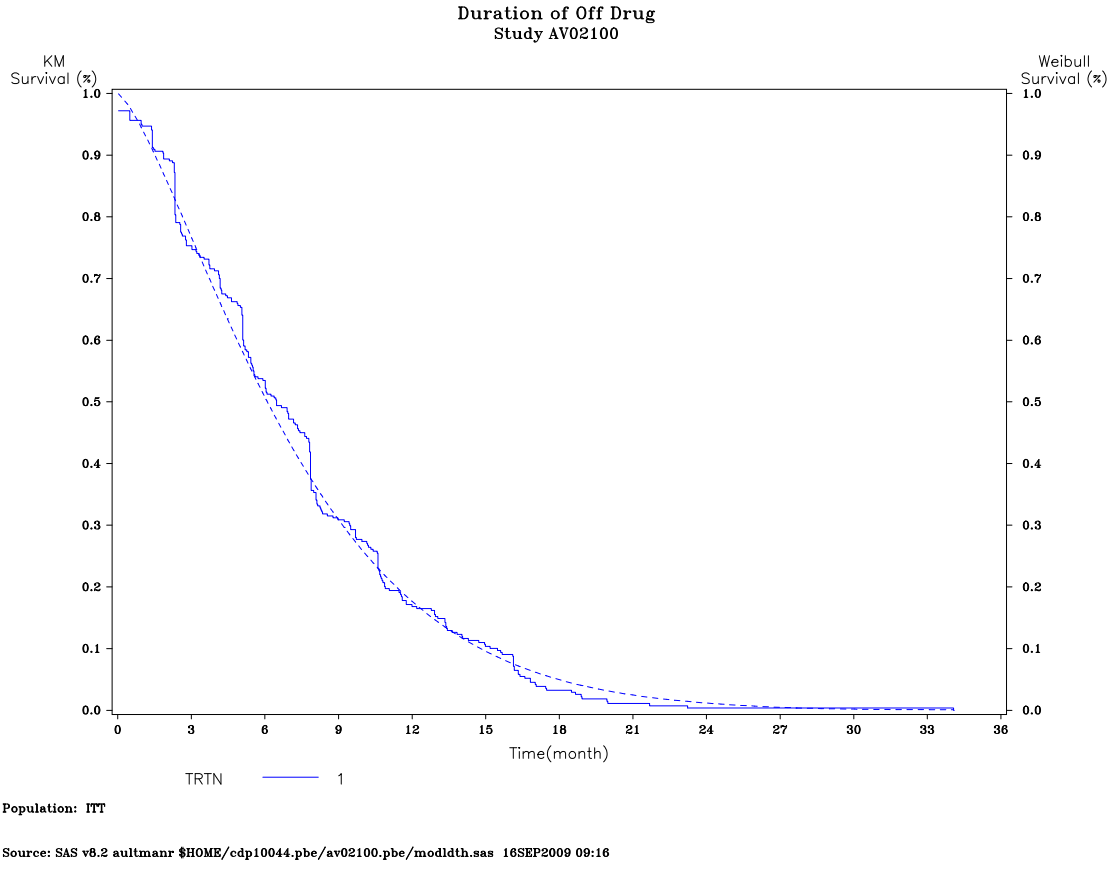
To be consistent with the definition of progression free survival, this “time to off treatment” was calculated as the time from randomisation until censoring or experiencing an event.

Time to off treatment was then modelled non-parametrically using Kaplan-Meier methods and parametrically with 5 distributional functions; Gompertz, Weibull, Exponential, Log Logistic, and Log Normal. Goodness of fit was assessed by AIC and BIC. The parametric model with the smallest AIC / BIC, the Weibull function for both treatments – see Table 29 and Table 30, was used in the economic model to reflect actual treatment (bevacizumab and/or paclitaxel) for each treatment arm.

Table 29: Summary of Parametric Functions' Goodness of Fit for BEV time of off treatment

Parametric Model	BIC / AIC BEV time to off treatment
Weibull	859.06 / 847.75
Exponential	886.64 / 882.87
Log Logistic	922.15 / 914.60
Gompertz	944.61 / 933.30
Log Normal	1009.43 / 1001.88

Figure 10. Extrapolated Time to off drug for bevacizumab (Weibull)

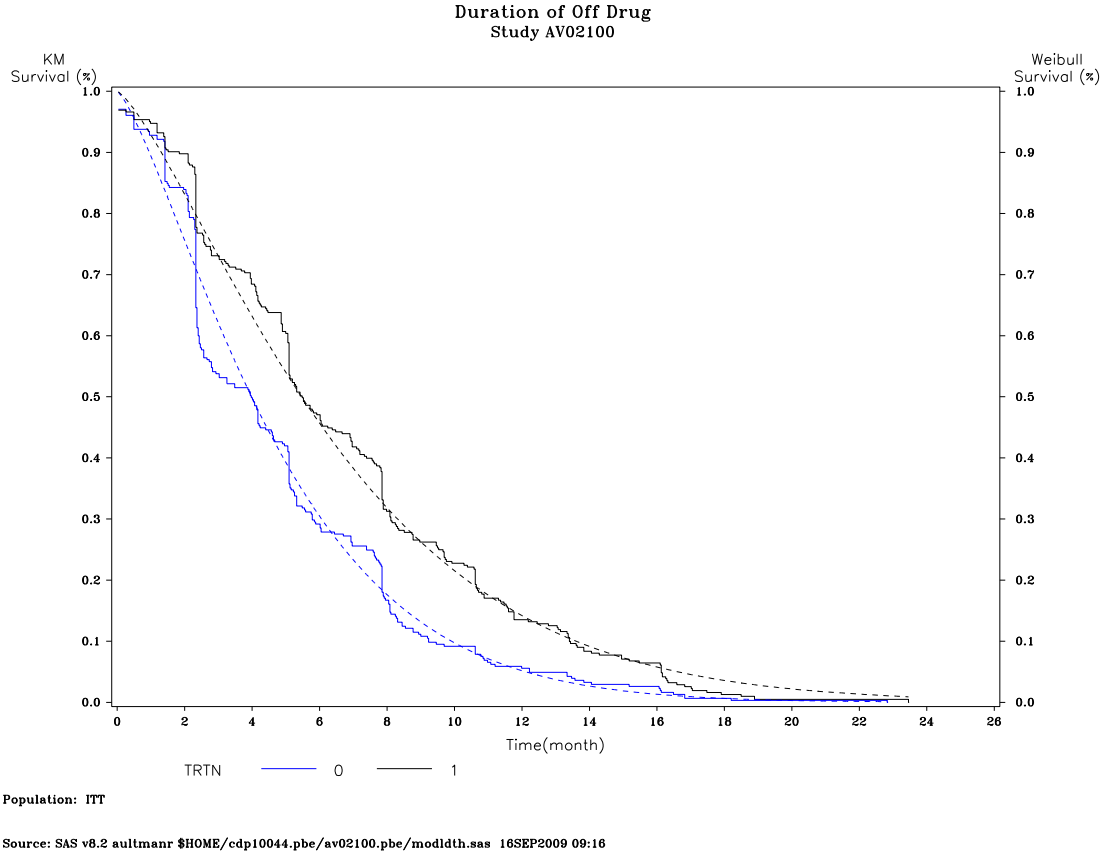


The assumption of proportional hazards was assumed for paclitaxel being that it was administered in both arms. Parametrically the assumption of proportional hazard implies that the difference observed in the the treatment arms was due to the addition of bevacizumab in the bevacizumab plus paclitaxel arm which can be considered reasonable since the randomisation was maintained when modelling time to off treatment. Patients that did not receive treatment were included with 0 days of treatment.

Table 30: Summary of Parametric Functions' Goodness of Fit for PAC time of off treatment

Parametric Model	**BIC / AIC** **PAC time to off treatment**
Weibull	1698.89 / 1681.11
Gompertz	1697.78 / 1684.45
Exponential	1751.49 / 1742.60
Log Logistic	1805.96 / 1792.62
Log Normal	1968.35 / 1955.02

Figure 11. Extrapolated Time to off drug for paclitaxel (Weibull)



*Note: Graph reflect paclitaxel administration where:

- TRTN = 0 (paclitaxel arm)
- TRTN = 1 (bevacizumab arm)

Diagnostic and residual plots were evaluated to substantiate the proportional hazard assumption. Being a treatment only model, the assumption of proportional hazards was evaluated with the diagnostic plots: (log(S(t)) vs Time and Log[-log(S(t))] vs Log (time). The Martingale and Deviance residuals were similarly evaluated for any evidence of a violation in proportional hazards however these plots are not very informative when treatment is the single model variate.

No assumption of proportionality was assumed for bevacizumab since it was administered in only the bevacizumab plus paclitaxel arm. The best fit to the modelled data was used to reflect bevacizumab dosing across the model's lifetime horizon.

Table 31. Weibull parameter estimates for time to off treatment

Time to off drug	Treatment arm	Lambda (λ)	Gamma (γ)
bevacizumab	Bev-Pac	0.05983343	1.354984449
paclitaxel	Bev-Pac	0.074099902	1.316438824
paclitaxel	Pac	0.112421713	1.316438824

Due to the absence of patient-level data, assumptions were required in order to model the time to off treatment for docetaxel and gemcitabine in combination with paclitaxel.

- Docetaxel: The docetaxel SPC states that docetaxel should be administered until disease progression but UK expert opinion and market research data show that it is administered for usually six cycles and no more than 9 cycles. Hospital sales data from IMS show that the average planned docetaxel treatment for metastatic breast cancer in UK is 6.13 cycles q3w, at an average planned dose of 150mg (or 88mg/m^2 for an average 1.7m^2 patient). An assumption was made in the model to allow for treatment until disease progression or a maximum of 6 months (or approximately 8.7 cycles) of treatment. When accounting for the rate of disease progression (described in Section 7.2.6.9), the average time on treatment was 4.86 months, equating to 7.0 cycles of treatment. Using a conservative dose of 75 mg/m^2 every 3

weeks, this was considered a reasonable representation of UK clinical practice.

- For gemcitabine + paclitaxel dosed as per SPC, it was assumed that time on treatment would be similar to that of paclitaxel monotherapy qw and therefore the comparator arm curve for 'time to off treatment' generated from E2100 was used as a proxy for this comparator's time on treatment.

7.2.2 Patients

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

The patient cohort within the economic evaluation is assumed to have the same baseline characteristics as those observed in E2100. As the trial represented the main registration study, it can be claimed that the economic evaluation is reflective of the licensed indication. The baseline characteristics of the trial are described in greater detail in Section 6.

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

No sub-group cost effectiveness analysis is presented. The E2100 study was not powered to show give significant results for patient subgroups. Consequently, any subgroup analyses are exploratory in nature. Furthermore, the licensed indication for bevacizumab is not restrictive in terms of the population and hence the intention to treat (ITT) population within the E2100 trial was considered the most appropriate population upon which to base the economic evaluation. It was also considered that

this population is representative of the patient group that will receive bevacizumab in the UK.

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

All subgroups showed a numerical improvement in PFS with bevacizumab (see forest plot provided in Figure 4 in Section 6). Two sub-groups, identified by their associated high level of unmet clinical need (patients with triple negative disease and patients previously treated with a taxane in the adjuvant setting) have previously been described (see section 4.1, 5 and 6.4). Patients with triple negative disease in E2100 had a 4.2 month improvement in median overall survival with addition of bevacizumab to paclitaxel, compared with a median life expectancy of 16.3 months for those treated with paclitaxel monotherapy. Patients treated with an adjuvant taxane in E2100 had an 8.7 month improvement in median overall survival with the addition of bevacizumab to paclitaxel, compared with a median life expectancy of 17.6 months in the paclitaxel monotherapy arm. However, as these sub-groups represent analyses outside of the final scope, these sub-groups will be not discussed in further detail.

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

Patients enter the evaluation at the start of treatment receiving either Bev-Pac or the comparator treatment (Pac, Doc, or Gem-Pac). Patients may only then exit the evaluation due to death from either the progression-free or progressed health states. Patients who failed to respond to either treatment will transition immediately to the progressed health state in the first cycle. The assumed points of entry and exit within the evaluation are the same for both treatment interventions. The risk of death from the progressed health state is modelled as a single population and calculated based on the E2100 trial. Details on these probabilities and the design of the model are described in more detail in Section 7.2.6.1 below.

7.2.3 Comparator technology

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

The comparators within the economic evaluation as definied by the final scope are

- paclitaxel (monotherapy) 90mg/m^2 weekly for 3 weeks followed by 1 week of rest (Study E2100),
- docetaxel (monotherapy) 75 mg/m^2 on day 1 every 21 days (current UK NHS clinical practice assumptions), and
- gemcitabine 1,250mg/m^2 days 1 and 8 plus paclitaxel 175 mg/m^2 on day 1 every 21 days (Albain et al. 2008).

The NICE-recommended first-line therapy for metastatic patients who are ineligible for anthracycline therapy is docetaxel monotherapy qw3.

Bevacizumab in combination with docetaxel has not been included as a *comparator* as it is not recommended nor used in the NHS and as mentioned previously, the cost-effectiveness of the *intervention* of bevacizumab in combination with docetaxel will be discussed briefly in Section 7.3.

7.2.4 Study perspective

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

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

7.2.5 Time horizon

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

The analysis took a lifetime time horizon (equating to a maximum of 10 years) as required by the NICE reference case in order to follow the vast majority of the original cohort of patients within the model to death (i.e. 99% of the cohort are estimated to

have died by this period in the two arms). This was to ensure all lifetime costs and benefits of both interventions could be evaluated.

7.2.6 Framework

7.2.6.1 a) Model-based evaluations

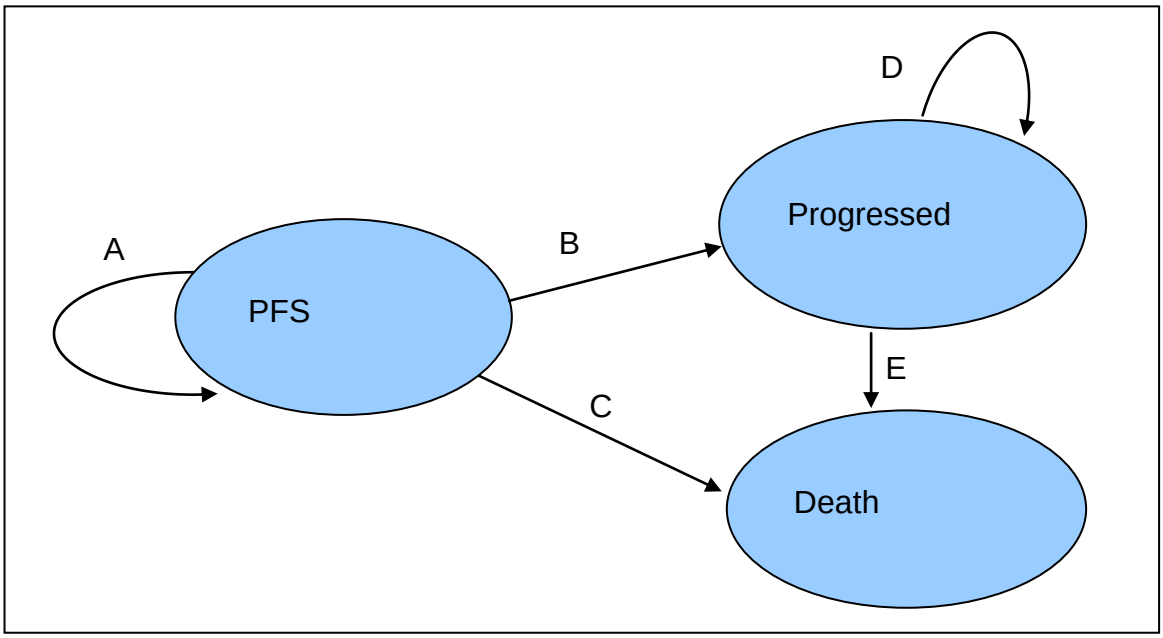
7.2.6.2 Please provide the following.

- **A description of the model type.**

The model captures the key outcomes of the E2100 clinical trial, and is designed for the purposes of extrapolating the trial outcomes beyond the last follow-up and accounting for future costs and clinical outcomes. The model is a 3-state Markov model constructed using Excel™ with a cycle length of 1 month, reflecting a very common structure for oncology economic evaluations. Patients are assumed to be within 1 of 3 possible discrete health states at any given time; “progression-free survival”(PFS), “progressed” or “death”. The “progressed” health state represents the time period from first treatment relapse until death and therefore includes the possible sequence of remission and relapse of second and following lines of treatments common to this disease area.

- **A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.**

Figure 12: Structure and transition probabilities of the Markov model



All patients were assumed to start in the progression-free health state which is defined by the inclusion criteria in the E2100 study protocol. At the end of each cycle a patient could either remain in PFS (A) or move to the progressed health state (B) or die (C). Once a patient is within the progressed health state, a patient may either remain within the progressed health state (D) or die at the end of each cycle (E). Patients could not move from the progressed health state back to PFS within the model. Death is an absorbing health state within the model. Monthly transition probabilities are listed in the table below with their exact derivation described in more detail in Section 7.2.6.8.

- **A list of all variables that includes their value, range (distribution) and source.**

Table 32. Model Parameters and Values

Model Variable	**Value**	**Source**
Transition Probabilities (tp)		
PFS to Progressed	Time dependent extrapolation under the assumption of proportional hazards with a Gompertz Gom(α_i,β), i= Bev-Pac, Pac) parametric function of PFS	E2100; Seidman 2008; Jones 2005; Albain 2006; Sparano 2008

	trial data. For the indirect comparisons against docetaxel and for gemcitabine + paclitaxel, it was assumed that the paclitaxel weekly arm from E2100 would be a reasonable proxy for the benefit of these treatments (informed in part by Section 6.6)	
PFS to PFS	1 – [tp(PFS to Progressed) + tp(PFS to death)]	E2100
PFS to death	Maximum value of either age-specific background mortality or monthly rate at which patients died (all cause) while in PFS	Office of National Statistics or E2100
Progression to Progression	1 - tp(Progression to death)	E2100
Progression to death	Constant hazard of dying obtained from modelling the E2100 post-progression population survival as a single population across both treatment arms	E2100
Patient characteristics		
Age	55.5	E2100
Weight	70kg	Assumption (same as NICE TA 34)
Body Surface Area	1.7 m^2	
Costs		
Supportive-care costs		
Monthly PFS health state supportive care • Background care • Assessment of response • After therapy	 • £165 • £72 • £43	Winstanley 2009; NHS reference costs, 2007/8; PSSRU 2008
Monthly Progressed health state supportive care • Background care • Last 14 days of life	 • £564 • £3,805	Winstanley 2009; NHS reference costs, 2007/8; PSSRU 2008
Monthly Drug costs		
bevacizumab	£3,592	BNF 58
docetaxel	£1550	BNF 58
paclitaxel weekly	£1176 / £99	BNF 58/PASA
paclitaxel every 3 weeks	£871 / £73	BNF 58/PASA
gemcitabine	£1038	BNF 58
Monthly administration costs		
bevacizumab + paclitaxel weekly	£896	NHS reference costs, 2007/8; PSSRU 2008; expert opinion;
paclitaxel weekly	£881	
docetaxel	£430	

gemcitabine + paclitaxel every 3 weeks	£795	BNF 58; SPC doc/pac
Adverse event costs		
Febrile neutropenia	£3803	NHS reference costs 2008/2009
Hypersensitivity	£274	NHS reference costs 2008/2009
Hypertension	£367	Coon 2008
Infection	£243	NHS reference costs 2008/2009
Peripheral Neuropathy	£0	Expert Opinion
Utilities – values		
PFS	0.73	Cooper et al. 2003; assumed the average of response and stable disease health states
Progressed	0.45	Cooper et al. 2003
Febrile Neutropenia	-0.21	Cooper et al. 2003 – assumed to be the difference between stable disease and febrile neutrapenia
Peripheral Sensory Neuropathy	-0.21	Brown 1998 – assumed to be the difference between stable disease and febrile neutrapenia
Discount rates		
Discount rates		
Costs	3.5%	Guide to Methods, NICE
QALYs	3.5%	Guide to Methods, NICE

The calculation for relevant values as well as further detail on the references is provided in the appropriate sections below. The assumed ranges for each model parameter are listed in Section 7.2.11.3 when describing the probabilistic sensitivity analysis (PSA). Further details on the calculation of costs is provided in Section 7.2.9.

- **A separate list of all assumptions and a justification for each assumption.**

1. The paclitaxel weekly PFS curve from E2100 was assumed to be a reasonable proxy for the docetaxel comparator and the gemcitabine + paclitaxel comparator
2. Patient level data was not available for the indirect comparisons and therefore assumptions on the time on treatment were made:
    a. Docetaxel comparator: Assumed treatment until progression or a maximum of 6 months (a maximum of 8.7 cycles of treatment) on a reduced dose (related to the docetaxel SPC) of 75 mg/m^2.
    b. Gemcitabine + paclitaxel comparator: the proportion of patients on treatment per model cycle was assumed to be the same for these comparators as the modelled time to off treatment for pacitaxel in the comparator arm.
3. It was assumed patients would have the same risk of dying post-progression regardless of the 1st line therapy received.
4. Following first relapse, all patients are assumed to have the same sequence of further health care resource including future lines of therapy (i.e. bevacizumab is not expected to change the subsequent treatment algorithm)
5. Costs and disutility values was included for adverse events with over 3% incidence in either treatment arm of E2100 as well as for febrile neutropenia which is commonly associated with docetaxel treatment

7.2.6.3 Why was this particular type of model used?

A Markov model was considered the most appropriate modelling approach as metastatic breast cancer is a chronic long-term disease which can be classified into a few discrete health states. The health states also mirrored the main endpoints measured in the phase III trials.

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

The structure of stratifying the clinical outcomes of oncology patients into progression-free, progression, and death is common practice in the economic evaluation of oncology. The health states align with one of the key objectives of treatment within this disease area: to place a patient into a progression-free health state for the longest period possible. Furthermore, the main outcomes of the clinical trial could be stratified into one of these 3 heath states: progression-free survival, progressed patients and death. Disease progression was represented by patients who were no longer classified as “progression free”, as defined by the E2100 protocol.

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

The main source that informed the model structure was the E2100 clinical trial for Bev-Pac and Pac. This trial provided the probability of a patient remaining within the PFS health state for each cycle of the model. Due to the very low number of events observed in the study for patients dying within the PFS health state, UK mortality rates were used to supplement the trial data sources. The indirect treatment comparison (described in Section 6.6) and the Sparano 2008 study was utilised to support the assumption that the E2100 paclitaxel weekly arm was a reasonable proxy for the docetaxel monotherapy and for gemcitabine in combination with paclitaxel comparisons. A single risk of death post-progression calculated from the combined populations in E2100 was used in the model for all treatment arms.

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

The 3 health states within the model capture most conditions relevant to the decision problem. A limitation of this modelling approach is that it is not aligned with the available utilities data in the setting of metastatic breast cancer. Utility values in mBC have generally been distinguished by the health states of response, stable disease, and progression where response and stable disease would both be classified as PFS. Due to this misalignment in model structure (which was driven by the primary

endpoint of PFS) and available utilities data in mBC (which is correctly focused on understanding how different response states impact on quality of life), we have attempted to adjust for the observed differences in utility values that occur within a single health state. This is described in section 7.2.8.

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

The cycle length of the Markov model is monthly. Clinical assessment and consequently diagnosed clinical status is rarely performed on a more regular basis than every month. Therefore it is unreasonable to assume that costs or clinical outcomes could change on a more frequent basis than every month.

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

Monthly half cycle correction was applied throughout the model's time horizon.

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

The primary analysis of the E2100 study was progression free survival with overall survival (OS) as a secondary endpoint. Progression free survival was modelled parametrically using a Gompertz function which was found to be the best fit to the data compared to other parametric functions (Table 34). Progression to death was modelled assuming a constant risk of dying (see Estimating Survival for Progressed Patients) estimated by modelling post-progression to death for all patients in E2100 that experienced at least one day or progression before dying or being lost to follow up. Post-progression therapies were not recorded in this study thus it is not possible to determine if the lack of significantly different survival in the bevacizumab treated arm is due to post-progression 2nd line treatment confoundment.

At the time of analysis 32.8% and 34.0% of patients in the paclitaxel and bevacizumab + paclitaxel arms of the E2100 study were still alive. Consequently, to estimate the lifetime clinical outcomes and associated NHS costs, assumptions of the future disease progression of these patients have been made.

Table 33. E2100 Results (based on 21 October 2006 cutoff)

E2100	Bev-Pac (N=368)	Pac (N=354)
Mean progression free survival (months) Median progression free survival (months) p value Log-Rank test Hazard ratio (unadjusted / unstratified) Hazard ratio (adjusted /stratified) Percentage of patients censored for overall survival	12.75 (se 0.6867) 11.33 P<0.0001 0.543 (CI 0.439-0.672) 0.483 (CI 0.385-0.607) 32.77%	8.64 (se 0.4977)) 5.82 33.97%
Mean overall survival (months) p value Log-Rank test	28.005 (se 0.9214) p=0.4392	26.323 (se 0.9477)

The clinical results reported on OS and PFS were non-parametrically (Kaplan-Meier) generated and were under the assumption of proportional hazards. Martingale and Deviance residuals were assessed to confirm that the assumption of proportional hazards was reasonable.

Figure 13. Progression Free Survival of Bev-Pac vs Pac (data cutoff 21OCT2006)

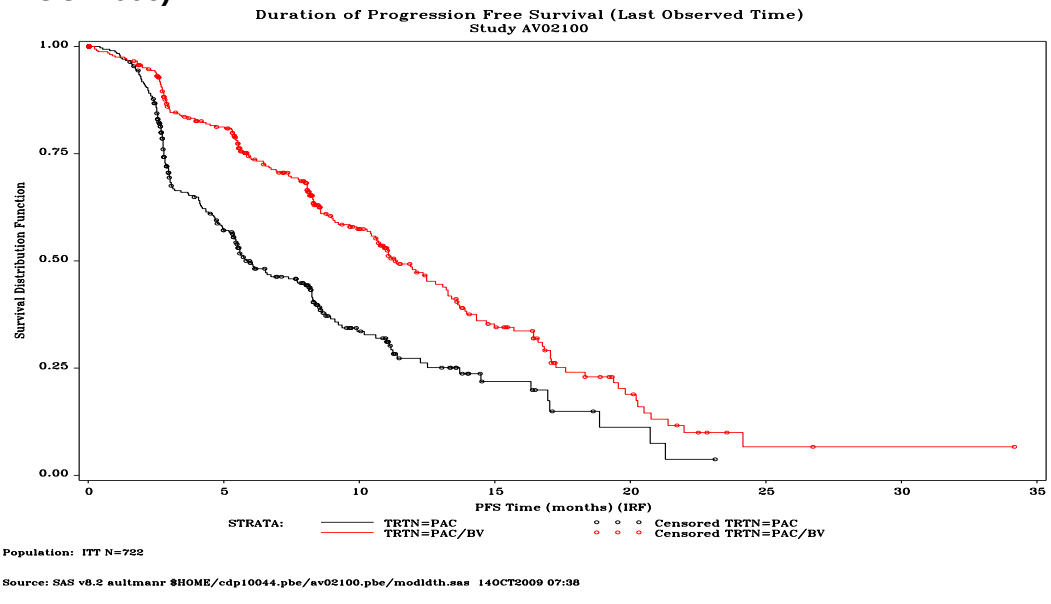
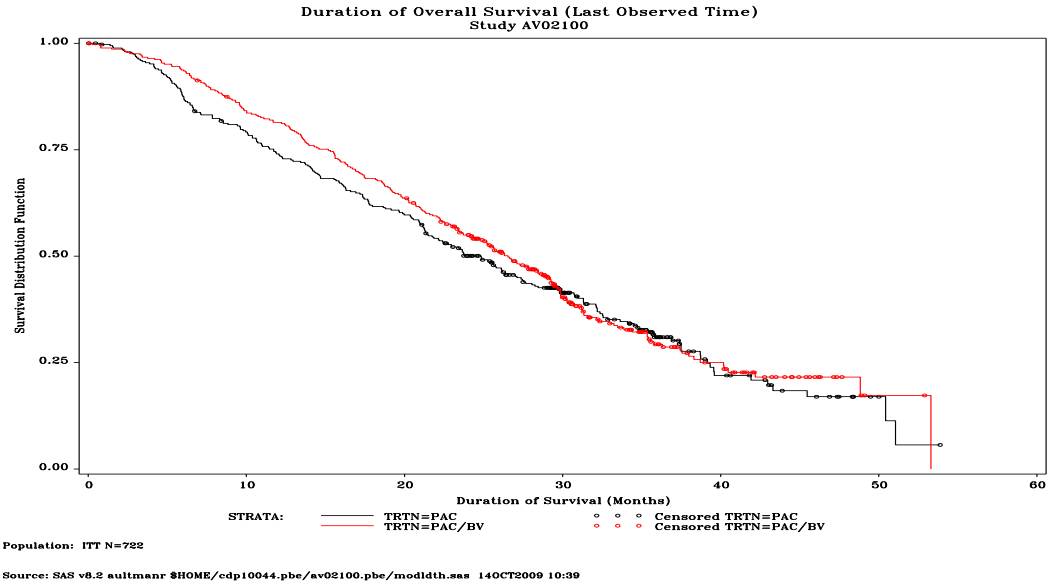


Figure 14. Overall Survival of Bev-Pac vs Pac (data cutoff 21OCT2006)



Extrapolation beyond the clinical follow up period can only be performed if one assumes that the data originated from a parametric distribution. The use of a parametric function requires that its unknown parameters (e.g. λ, γ parameters of a Weibull survival function) can be estimated. Various parametric functions were available and each function was assessed for its goodness of fit to the data using Akaike (AIC) and Bayesian Information Criteria (BIC), the mean squared deviance and graphical inspection of fit (e.g., Martingale residuals) to the data before deciding on the final functional form. The parametric model structures assessed for goodness of fit to the data were: Log Logistic, Weibull, Log Normal, Gompertz, Exponential and the Generalised Gamma.

- **Estimating long-term Progression-free survival**

Bevacizumab + paclitaxel and paclitaxel monotherapy

To estimate future progression free survival (PFS) an extrapolation of the PFS curve from the E2100 study for Bev-Pac and Pac was performed. A monthly, treatment- and time-dependent probability of remaining within the PFS health state could then be calculated from these extrapolated curves to populate the Markov model (transition probability A and B from Figure 12).

Extrapolation of the progression free (PFS) data was carried out under the assumption that the data originated from a parametric distribution. The parameters were estimated using patient level clinical data from the E2100 study (21 October 2006 data cut). Six parametric functions were assessed for goodness of fit to the data. A proportional hazards Gompertz function was found to be the best fit to the PFS data was based on the AIC / BIC for PFS and graphical inspection of the fit. A relaxation of proportional hazards are indicated whenever there is evidence that the shape of the treatment arms differ. There was no indication of differences in the shapes of the treatments and no violation of the underlying assumption of proportional hazards was noted in the diagnostics (e.g. Martingales) plots. Thus a proportional hazards (same shape parameter) Gompertz model was selected as the best fit parametric function to model the PFS data. Table 34 gives the goodness of fit results for PFS for all functions evaluated. Albeit an inferior method for assessing a function's goodness of fit to the data, mean squared deviation (MSD) is also herein reported.

Table 34: Summary of Parametric Functions' Goodness of Fit for PFS

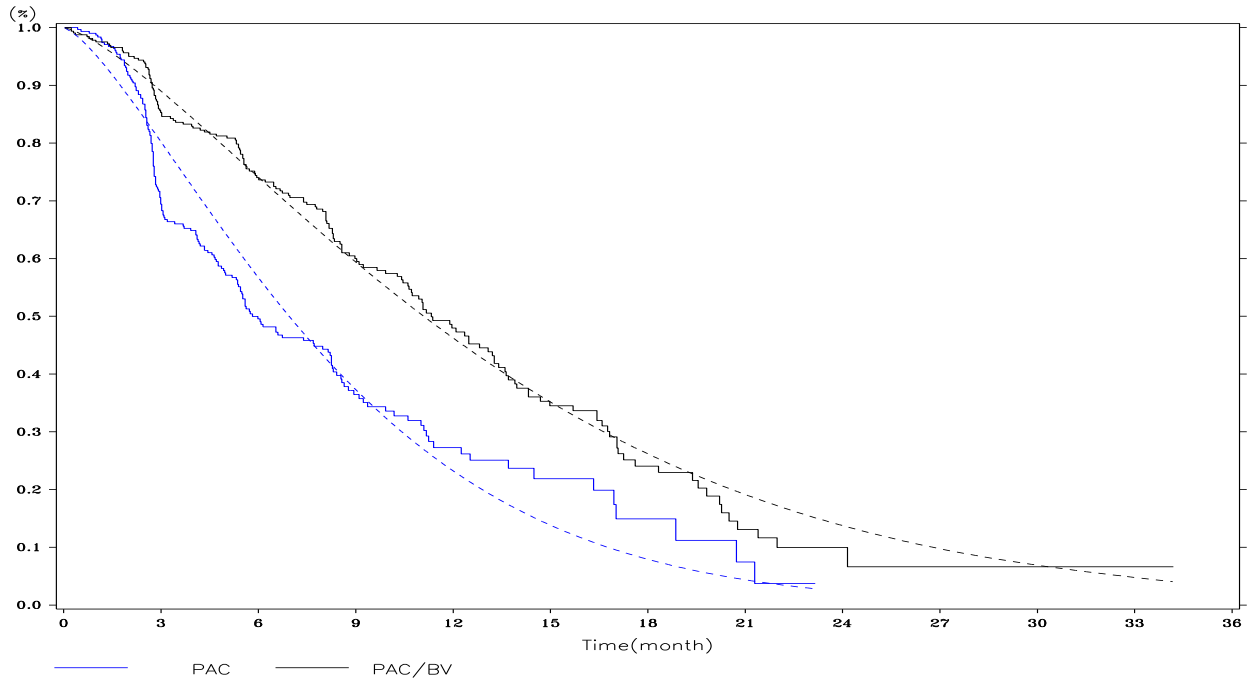
Parametric Model	**Bev-Pac vs Pac Alone BIC / AIC (MSD: Bev-Pac / Pac) Progression Free Survival**
Exponential	1408.32 / 1399.16 (0.02978 / 0.003147)
Log Logistic	1357.28 / 1343.53 (0.00183 / 0.005544)
Generalized Gamma	1361.37 / 1343.04 (0.00197 / 0.000352)
Log Normal	1362.99 / 1349.25 (0.00895 / 0.002967)
Weibull	1374.27 / 1355.94 (0.00103 / 0.008718)
Gompertz	1260.24 / 1246.49 (0.00169 / 0.008830)

The Gompertz survival function is defined as

$$S(t) = \exp(\frac{\lambda}{\gamma}(1 - \exp(\gamma t))), \quad t \geq 0$$

The probability of staying in this health state is determined by the cumulative ½-cycle corrected survival probabilities obtained from Gompertz function for PFS. Figure 15 represents the KM PFS curves from E2100 and extrapolated PFS curves for bevacizumab + paclitaxel and paclitaxel using the Gompertz function. The impact on the ICERs of using alternative parametric curves was explored in the sensitivity analysis.

Figure 15. Extrapolated Progression Free Survival of Bev-Pac vs Pac (Gompertz)



Indirect Comparisons: docetaxel and gemcitabine+paclitaxel

A systematic review was performed to identify the relevant RCTs that used docetaxel and gemcitabine + paclitaxel for the treatment of metastatic breast cancer. The trials necessary to link the relative treatment benefit of docetaxel and of gemcitabine in combination with paclitaxel were limited in their quality and/or relevance to UK clinical practice. In particular, the Seidman 2008 study (necessary to link weekly to 3-weekly paclitaxel) appeared to have an imbalance of trastuzumab treated patients, the Jones 2005 study (necessary to link 3-weekly paclitaxel to 3-weekly docetaxel) utilised a higher docetaxel dose (100mg/m^2 compared to the UK standard of 75 mg/m^2) and considerably longer duration (up to 32 cycles compared to the UK norm of 6 cycles) and finally the Albain 2008 study (necessary to link gemcitabine + paclitaxel to 3-weekly paclitaxel) used the inferior paclitaxel administration regimen of 3-weekly cycles.

Despite these limitations, an informal indirect treatment comparison was presented to understand the potential relationship between the weekly paclitaxel regimen represented in he E2100 study and the two other comparators of interest (docetaxel

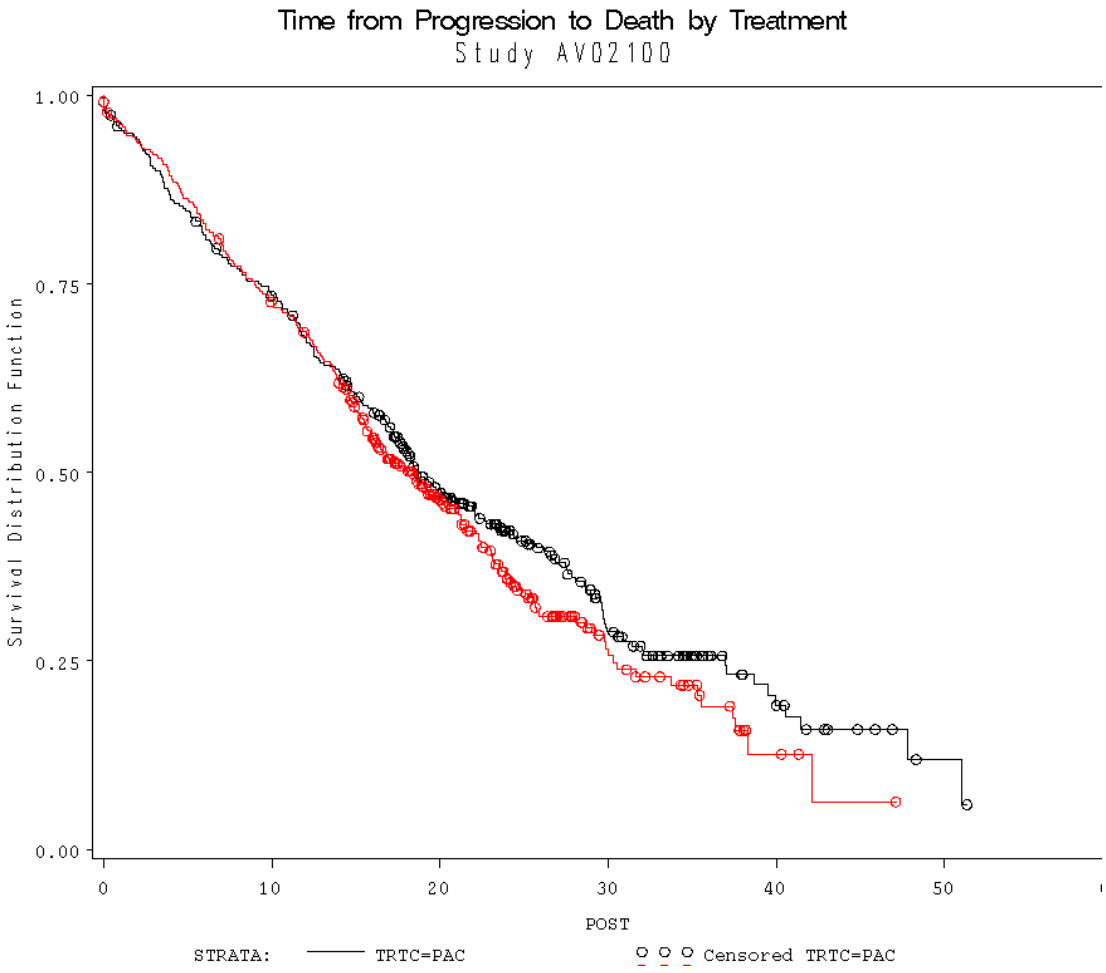
and gemcitabine+paclitaxel) (see Section 6.6). The findings of both indirect comparisons resulted in insignificant hazard ratios for the relative treatment benefit of paclitaxel weekly relative to docetaxel (HR=1.147 95%CI(0.89-1.48)) and relative to gemcitabine + paclitaxel 3 weekly (HR=0.958 95%CI(0.76-1.21)).

For the direct comparison of weekly paclitaxel with 3-weekly docetaxel, the only head-to-head evidence in breast cancer of the relative treatment benefit is the large adjuvant study of Sparano (2008). In this study, paclitaxel qw gave the highest 5-year DFS and OS (81.5% and 89.7%), followed by docetaxel q3w (5-year DFS 81.2% and OS 87.3%). This suggests that the treatment benefit of these two regimens is non-significantly different from one another. This fact in combination with the non-significant hazard ratio derived from the weak indirect treatment comparison mentioned above, suggested that the E2100 PFS curve for weekly paclitaxel would be a reasonable proxy for the treatment benefit associated with 3-weekly docetaxel. It was also assumed that this would hold true from the gemcitabine + paclitaxel combination due to the similarly non-significant hazard ratio of 0.958 from the weak indirect comparison of paclitaxel weekly compared to gemcitabine + paclitaxel.

- **Estimating Survival for Progressed patients**

The progressive health state is defined by surviving patients having experienced disease progression. Patients will transition from this state to the absorbing state (Death) at an assumed constant rate determined by having modelled progression to death for patients having experienced at least one day of progression before dying or being censored. The patients in the progressive health state were first stratified by protocol treatment regimen (Bev-Pac or Pac Alone) and assessed for treatment differences using the Kaplan-Meier method. The log-rank was found non-significant (p=0.2441) for treatment differences (Figure 14). The relevant Kaplan Maier curves for this analysis are illustrated below. By the overlapping nature of these curves and non-significant log-rank test, it was considered a reasonable assumption to assume an equal risk of death for Bev-Pac and Pac patients following disease progression.

Figure 16. Post Progression Survival by Treatment (E2100 21 October 2006 data cutoff)



A simple Markov process was chosen to model progression to death. The rate of death of progressed patients was calculated by regressing the log of the Kaplan-Meier survival probabilities by time using ordinary least squares methods with the calculated rate of death taken from the estimate of the time parameter. The progression to death population was modelled as a single population with the mean time to death converted to a constant hazard of dying (as described above, this was considered appropriate due to the non-significant log-rank for treatment differences for overall survival from progression to death). The original single population KM and the resulting extrapolated curve are provided in Figure 17. The resulting probability of death was applied to all patients irrespective of the choice of 1st line therapy.

Figure 17. Overlay of KM curve on extrapolated progression to death (assuming one population / no difference in risk of death post progression)

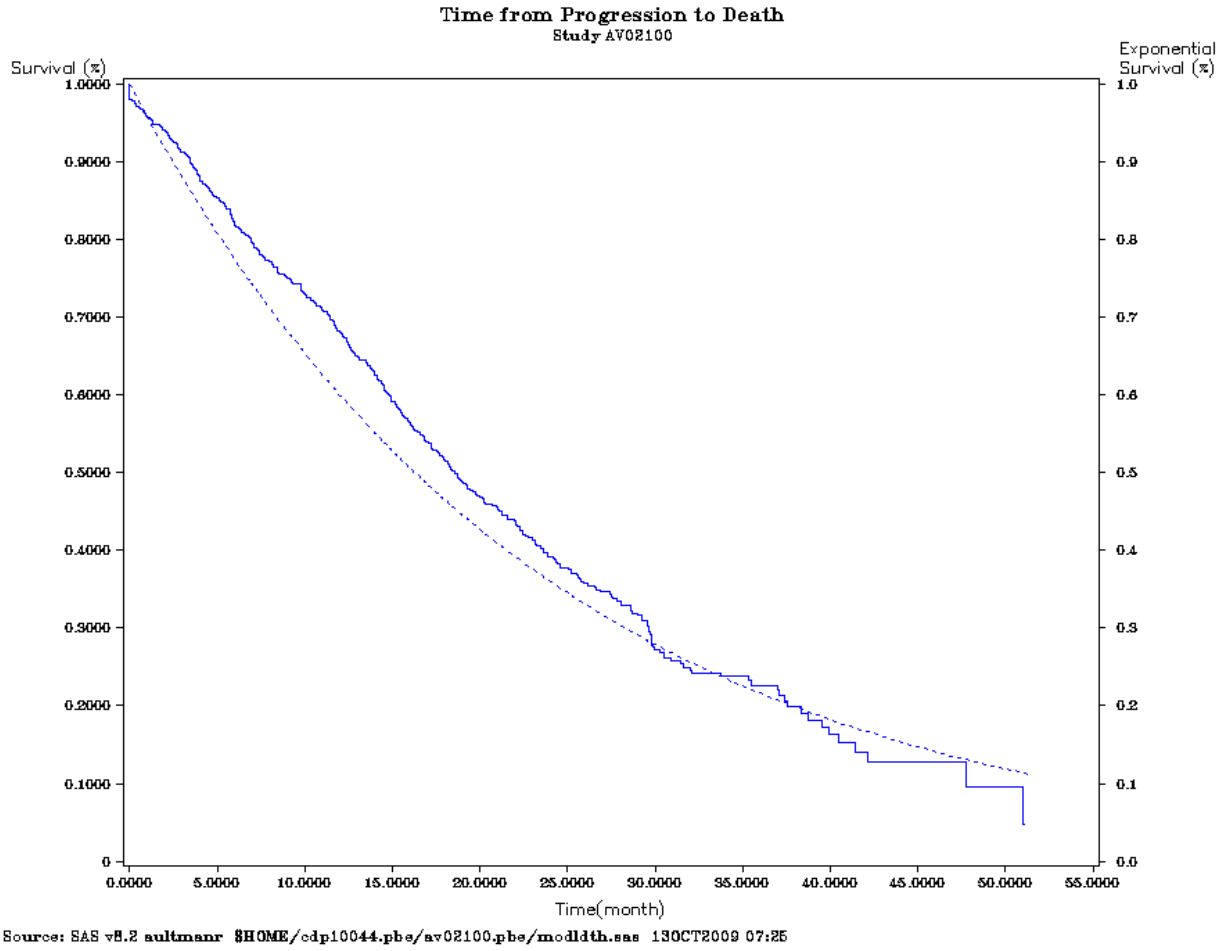


Table 35. Post-Progession Rates & Probabilities of Death for all 1st line treatment comparators

	Post-progression as a single population
LET	-0.04351492
Standard error	0.00033198
Constant monthly rate of death	0.042581731
Constant monthly probability of death	0.041687861

- **Estimating death in progression-free survival**

This state includes those patients who died from any cause (standard UK all-cause background mortality) or due to advanced disease. No costs are attached to the death health state and the utility attached is zero. A number of patients die while in PFS and, along with those patients that die while in progression, will collectively

represent the total number of deaths in the Markov process. The methodology employed for patients dying while in the progression health state has been described above.

The number of patients that die, expressed as a monthly rate, while in PFS is determined by either background mortality or by the monthly rate at which patients died (any cause) while in PFS from the E2100 trial. For example, 19 of the 368 patients in the Bev-Pac arm died while in PFS. These deaths occurred over a period of 24 months. The rate of death in the Bev-Pac arm is calculated as the number of PFS deaths divided by the PFS person months; 19 / 2764.63 = 0.006872529. The monthly number of patients that die while in PFS is then the maximum of either background mortality or the monthly probability of death calculated as 1 – exp(-rate of death) = 0.006872529. The rate approximates the probability when it is very small. This approach was preferred to utilising the trial data alone; due to the low number of events in E2100 study, it seemed unreasonable to assume that mortality rates would at times be lower than the average all cause mortality rate. Background mortality was taken from UK national statistics. The PFS mortality rates for paclitaxel were used as a proxy for the mortality rates expected for docetaxel and gemcitabine+paclitaxel. Rates of death from the progressive disease state were described in the previous section. The monthly probabilities of death from both PFS and progressive disease are presented in the table below.

Table 36. Transition probabilities for mortality rates

Markov Transition	Monthly probability	Data source & additional assumptions
PFS to death	Bev-Pac = 0.006872529	Maximum of age-specific background mortality (National Statistics) or monthly rate at which patients died while in PFS from the E2100 study
	Pac = 0.0179967	The same mortality rate for PFS to death from the paclitaxel control arm was assumed for docetaxel and gemcitabine in combination with paclitaxel
Progression to death	One population= 0.041687861	(1) Base case: Progression to death population from E2100 treated as a single population with mean time to death converted to a constant hazard of dying regardless of treatment arm
	Bev-Pac = 0.044775226	(2) Sensitivity Analysis: Progression to death population by treatment arm with mean time to death converted to a constant hazrd of dying. Paclitaxel monotherapy probability of death used as a proxy for docetaxel and gem-pac probability
	Pac = 0.039806776	

7.2.6.10 b) Non-model-based economic evaluations

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

7.2.7 Clinical evidence

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

Assuming that the "baseline risk" of disease progression relates to the comparator treatments within the evaluation, this was derived directly from the E2100 trial results for paclitaxel.

7.2.7.2 How were the relative risks of disease progression estimated?

The probability of moving from PFS to the Progressed health state and death are described in section 7.2.6.8 above.

7.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how

was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The health state of progression free survival and ”progressed” were linked to the final outcome of QALYs in the model. The utility scores were informed by an estimate from the literature in patients requiring first-line treatment for metastatic breast cancer (see Section 7.2.8.3).

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

Health outcomes associated with adverse events observed in E2100 whilst on treatment were included in the model for those events occurring in at least 3% of patients as well as febrile neutropenia. The most frequent adverse events (greater than 3%) were the following: hypersensitivity, hypertension, infection, peripheral sensory neuropathy. Cost and disutilities were incorporated into the model where possible.

As docetaxel is associated with a significant incidence of febrile neutropenia it was incorporated as an adverse event in the docetaxel model arm. It was assumed that the docetaxel adverse events would be equivalent to those for pacliaxel with the exception of this increased incidence of febrile neutropenia. The results of the Decision Support Unit’s review of Febrile Neutropenia incidence in support of the NICE evaluation of erlotinib (in TA162) were used to inform the incidence of Febrile Neutropenia in the model. It was assumed that the rate of Febrile Neutropenia, given an equivalent dosing schedule (75mg/m^2), would be approximately the same irrespective of whether patients were being treated for breast or lung cancer.

As docetaxel is typically perceived as having a worse toxicity profile than paclitaxel the assumption that docetaxel AEs are equivalent to those for paclitaxel (with the exception of febrile neutropenia) may be a conservative assumption and will likely over-estimate the ICER between bevacizumab in combination with paclitaxel versus docetaxel.

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

No expert opinion was used to estimate clinical parameters. However, expert opinion was used to determine some NHS resource utilisation. This includes the assumption of pharmacist time required to prepare different chemotherapy regimens. These are described further in Section 7.2.9.2.

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

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

7.2.8 Measurement and valuation of health effects

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

Health benefits were expressed as QALYs within the model.

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

The economic analysis considers the utility of individuals with metastatic breast cancer associated with the model health states; progression free survival (response or stable disease), and progressed disease. Moreover, the analysis considers disutility of adverse events corresponding to febrile neutropenia and peripheral sensory neuropathy.

7.2.8.3 How were health effects measured and valued?

A focused literature review identified a number of studies with information on the likely utility of breast cancer patients (Berger 2003, Bocci 2005, Brown 1998, Brown 2001, Cooper 2003, Chung & Carlson 2003, De Cock 2005, Geels 2000, Guest 2005, Hutton 1996, Jones 2004, Karnon 2007, Launois 1996, Lloyd 2006, Remak & Brazil 2004, Romanus 2004, Shaughnessy 2002, Takeda 2007, Verma 2005, Vu 2008).

The identified studies were economic analyses (14), methods review (2), and other citations involving management of breast cancer (4). Not all studies had information on patient utility. Table 37 presents a summary of the main studies with corresponding utility values. It should be noted that all utility studies identified used the standard gamble elicitation approach and therefore do not meet the NICE-prefered technique of time trade off.

Table 37. Utility values for health states available from the literature

Study name	Winstanley 2009**	Lloyd 2006	Brown 2001*	Brown 1998		Hutton 1996		Launois 1996
Type of study	Pooling of utilities from different sources (all derived from oncology nurses using the Standard Gamble technique). Country not specified	Utility study (SG) **100** member of the public. UK[¥]	Utility study (SG) **30** oncology nurses, UK	Utility study (SG) **29** oncology nurses. US	Utility study (SG) **154-179** oncology nurses. US, Germany, Italy, Netherlands, Spain, UK	Utility study (SG) **30** oncology nurses. UK	Utility study (SG) **129** oncology nurses. UK, Germany, Italy, Spain, US and Canada	Utility study (SG) **20** nurses. France
Response								
No toxicity	**0.8100**	0.7910	0.8400 (0.12)	0.8400	0.8100	0.8400[$]	0.8100[$]	0.8100
Peripheral neuropathy				0.5800	0.5600			
Febrile neutropenia		0.6610	0.6200 (0.16)					
Febrile neutropenia requiring hospitalisation				0.4200	0.3000			

Study name	Winstanley 2009**	Lloyd 2006	Brown 2001*	Brown 1998		Hutton 1996		Launois 1996
Diarrhoea/vomiting		0.7038						
Stomatitis		0.6603						
Fatigue		0.6930						
Hand and foot syndrome		0.6921						
Neutropenia								
Hair loss		0.6941						
Neuropathy						0.6200	0.5300	0.5700
Oedema			0.7800 (0.15)	0.8200	0.7600	0.7800	0.7500	0.7400
Skin condition			0.5600	0.6500	0.5600			
Stable Disease								
No toxicity	**0.6500**	0.7150	0.6200 (0.22)	0.7000	**0.6500**	0.6200	0.6200	0.7500
Peripheral neuropathy				0.4100	**0.4400**			
Febrile neutropenia		0.5650						
Febrile neutropenia requiring hospitalisation	**0.4400**							
Diarrhoea/vomiting		0.6130						

Study name	Winstanley 2009**	Lloyd 2006	Brown 2001*	Brown 1998		Hutton 1996		Launois 1996
Stomatitis		0.5643						
Fatigue		0.6005						
Hand and foot syndrome		0.5995						
Neutropenia								
Hair loss		0.6019						
Neuropathy								0.5000
Oedema				0.6800	0.6200			0.7300
Progressive Disease - no toxicity	**0.4500**	0.4440	0.3300 (0.24)	0.4900	0.3900	0.3300	0.4100	0.6500

* (Std Deviation)

**Winstanley 2009 refers to values from Cooper et al. 2003

¥ Estimated based on patient aged 38.2 to match UK census data

§ Described as partial response

The base case analysis follows the assumptions of Winstanley & Murray (2009) and applies utilities as identified by Cooper et al. (2003) with the inclusion of Brown 1998 study to inform the disutility associated with peripheral sensory neuropathy. Additional scenario analyses regarding utility estimates were also considered (described in Section 7.2.11.2 below). The base-case utility scores are presented in Table 38. These values have been used for all treatments. In reality it is likely that the quality of life whilst treated with docetaxel could potentially be much worse, given the toxicities associated with this treatment.

Table 38. Base-case analysis utility scores

Health state	Utility score	Reference
Response	0.81	Winstanley 2009 / Cooper 2003
Stable disease	0.65	Winstanley 2009 / Cooper 2003
Progression-free survival	0.73	Assumption: average of response and stable disease
Progressive disease	0.45	Winstanley 2009 / Cooper 2003
Disutility from febrile neutropenia	-0.21	Winstanley 2009 / Cooper 2003 derived from stable disease health state applid in month 1 only
Disutility from peripheral sensory neuropathy	-0.21	Brown 1998 derived from stable disease health state applid in month 1 only

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

Quality of life was measured in the E2100 trial, however these data are not currently available for further analysis other than that already provided in Section 6.4. However as these represent disease specific instruments (FACT-B); they are not adequate for informing the requisite generic measure of health or subsequent utility scores.

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

All those events with fewer than 3% frequency in both arms of the E2100 trial were excluded from consideration, with the exception of febrile neutropenia due to its associated with docetaxel treatment. The economic analysis excludes any health effects (disutilities) from adverse events other than febrile neutropenia or peripheral neuropathy. It was assumed that the remaining adverse events would not have a notable impact to the model results, and furthermore the literature did not provide any suggested disutility scores for most of the remaining adverse events.

7.2.9 Resource identification, measurement and valuation

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

Costs associated with drug administration

- Drug costs for Bev-Pac, Pac, Doc, and Gem-Pac
- Drug administration costs for Bev-Pac, Pac, Doc, and Gem-Pac
    - Administration cost
    - Consultation cost (face-to-face with clinician)
    - Hospital pharmacist time for drug preparation
    - Pre-medication costs

The economic analysis considers resource use relevant to the management of the disease from an NHS and PSS perspective:

- Diagnostic test computerized tomography (CT scan)
- Consultant outpatient visits
- GP surgery visits
- GP home visits
- Community nurse home visits
- Clinical nurse specialist cost
- Therapist cost

The following section describes each resource in detail.

7.2.9.2 How were the resources measured?

The sources for resource utilisation are the published literature (Winstanley & Murray 2009, Coon 2008, NICE DSU 2007), BNF 58 and a national cost dataset (NHS reference costs, 2008).

1) Drug costs for Bev, Pac, Doc, and Gem

Drugs costs were calculated according to the recommended adult dose and wastage was assumed for all therapies. Duration of treatment was estimated from the E2100 trial as described in section 7.2.1.2. Dose reductions were not modelled although these can be common among these treatments. The rationale for this approach is due to the lack of comparable data across the different trials. The average weight of a 1st line metastatic breast cancer patient was assumed to be 70kg and corresponded with a body surface areas of 1.7m2.

Table 39. Drug doses and costs for bevacizumab

Assumptions	Value	Description
Body weight in kilograms	70	Assumption (same as NICE TA 34)
Unit price per vial (£) • 100mg • 400mg	 242.66 924.40	BNF 58
Recommended dose (mg/kg)	10	Recommended adult dose as per SPC; E2100
Average adult dose (mg) including wastage	700	10mg/kg * 70kg = 700mg
Cost per infusion (£)	1,652	400mg@£924.40 + 3*100mg@£242.66
Number of infusions per month	2.17	28 days per cycle; 30.4375 days per month. 2 administrations per cycle * 1.08705 cycles per month
Total drug cost per patient (£) per month	**£3,592**	£1,652 cost per infusion * 2.17 infusions per month

Table 40. Drug doses and costs for paclitaxel

Assumptions	Value (for Bev-Pac and Pac arms)	Value (for Gem-Pac arm)	Description
Body surface area m^2	1.7		Assumption (same as NICE TA 34)
Unit price per vial (£) • 150mg (list price) • 150mg (average PASA price)	• £300.52 • £25.28[1]		BNF 58 (non-propriety) PASA Pharmaceuticals electronic Market Information Tool
Recommended dose (mg/ m^2)	90	175	E2100
Average adult dose (mg) including wastage	180mg	300mg	90mg/ m^2 * 1.7 m^2 = 153 175mg/m^2 * 1.7 m^2 = 297.5 Both are rounded up to nearest vial size
Cost per infusion (£) • 150mg (list price) • 150mg (average PASA price)	£360.62 £30.34	£601.04 £50.56	180mg/150mg * pac price 300mg/150mg * pac price
Cycle length (in days)	28	21	
Number of infusions per cycle	3	1	
Number of infusions per month	3.26	1.45	30.4375 days per month 3 administrations per cycle *1.08705 cycles per month 1 administrations per cycle *1.44940 cycles per month
Total drug cost per patient (£) per month • 150mg (list price) • 150mg (average PASA price)	**£1176** **£99**	**£871** **£73**	Cost per infusion * number of infusions per month

[1] This represents the average (weighted arithmetic mean) price paid for paclitaxel over the last four months of the period ending April 2009

Table 41. Drug doses and costs for docetaxel and gemcitabine

Assumptions	Doc	Gem (for Gem-Pac arm)	Description
Body surface area m^2	1.7		Assumption (same as NICE TA 34)
Unit price per vial (£): (80mg for docetaxel; 1 gram for gemcitabine)	534.75	162.76	BNF 58
Recommended dose (mg/ m^2)	75	1,250	SPC; UK Clinical Practice
Average adult dose (mg) including wastage	160mg	2,200mg	75mg/ m^2 * 1.7 m^2 = 127.5 1250mg/m^2 * 1.7 m^2 = 2125 Both are rounded up to nearest vial size
Cost per infusion (£)	£1070	£358	180mg/80mg * doc price 2.2g/1g * gem price
Cycle length (in days)	21		SPC
Number of infusions per cycle	1	2	SPC
Number of infusions per month	1.45	2.90	30.4375 days per month Number of administrations per cycle * 1.44940 cycles per month
Total drug cost per patient (£) per month	**£1550**	**£1038**	Cost per infusion * number of infusions per month

2) Drug administration costs for Bev, Pac, Doc, and Gem

All costs described below are applied in the model for the duration to time on treatment (see Section 7.2.1.2).

a. Administration cost

To estimate the resource utilisation associated with the drug administration of bevacizumab and the comparators, the appropriate reference costs (National Schedule of Reference Costs 2007-08) associated with “daycase and regular day / night” chemotherapy administration were utilised. All therapies (monotherapys and combination therapies) were considered to fall within the category of “more complex parenteral chemotherapy”).

Table 42. Drug Administration costs

Applied to:	HRG label (Code)	National average unit costs
bevacizumab in combination with paclitaxel	Deliver more complex Parenteral Chemotherapy at first attendance	£237
paclitaxel monotherapy		
docetaxel monotherapy		
gemcitabine in combination with paclitaxel		

b. Pre-medication costs

According to their SPC, docetaxel and paclitaxel should be provided after certain pre-medications are administered.

For docetaxel in mBC, it is recommended that 8 mg (4 x 2 mg tablets) dexamethasone twice a day for 3 days (day before administration, day of administration, day after administration) be provided. The regimen requires a total of 24 x 2 mg dexamethasone tablets. BNF 58 cost of dexamethasone is £7.19 for a 50 tab pack of 2 mg tablets (14.38p per tab) or £13.92 for a 100 tab pack of 2 mg tablets (13.92p per tab). If costed at per tab rate this equates to a dexamethasone course £3.34 at the 100 tab pack rate or £3.45 at the 50 tab pack rate. The lower cost of £3.34 is assumed.

For paclitaxel in mBC, it is recommended that all patients must be given pre-medication consisting of corticosteroids, antihistamines and H2-receptor antagonists

prior to paclitaxel administration, in order to prevent severe hypersensitivity reactions. The following costing exercise was conducted.

Dexamethasone:

- Total 20 mg (10 x 2 mg tablets) dexamethasone administered approximately 12 and 6 hours before paclitaxel.
- BNF 58 cost of dexamethasone is £7.19 for a 50 tab pack of 2 mg tablets (14.38p per tab) or £13.92 for a 100 tab pack of 2 mg tablets (13.92p per tab).
- If costed at per tab rate this equates to a dexamethasone course costing:
    - £1.44 at the 50 tab pack rate
    - £1.39 at the 100 tab pack rate
- The lower cost of £1.39 is assumed

Diphenhydramine:

- 10 mg IV 30-60 minutes before paclitaxel. BNF 58 cost of diphenhydramine is £1.62 for a 1 ml ampoule (with 10mg/ml concentration).

Ranitidine:

- 50 mg IV 30-60 minutes before paclitaxel. BNF 58 cost of ranitidine is £1.07 for a 2 ml ampoule (with 25mg/ml concentration)

Total paclitaxel accompanying medication cost: £1.39 + £1.62 + £1.07 = **£4.08**

No pre-medications are noted in the SPC for bevacizumab or gemcitabine.

Table 43. Premedication costs per administration

Treatment	Pre-medication cost per administration
Bevacizumab	£0
Paclitaxel	£4.08
Docetaxel	£3.34
Gemcitabine	£0

c. Pharmacist time costs

Expert advice was sought regarding time required for pharmacist to prepare each of the regimens above. It was assumed that each therapy would take 15 minutes to prepare, and therefore days when two treatments (Gem-Pac in Week 1; Bev-Pac in

Weeks 1 and 3) were required, it would take 30 minutes to prepare the regimen. The cost of a hospital pharamacist (without qualifications) per hour was assumed to be £28 (PSSRU 2008).

d. Response assessment costs

Response assessment is assumed to involve a consultant led attendance and one CT scan every three months (Winstanley 2009). The associated cost is £71.88 per month and it is not assumed to differ by treatment regimen. This is based on a unit cost of £86 for a Clinical Oncology - consultant led: follow-up attendance non admitted face to face visit and £130 for a Computerised Tomography Scan, two areas, with contrast – outpatient (National Reference Costs 2007/2008).

3) Supportive care cost

a. Background management during PFS

The model assumes that background management of non-progressive breast cancer involves 2 nurse home visit per month, 1 GP visit (including direct care staff) per month, and 1 clinical nurse visit per month (Winstanley 2009). The associated cost is £165 per month and it is not assumed to differ by treatment regimen. This is based on a unit cost of £46 for General practitioner unit cost including direct care staff costs without qualifications; £23 for Community nurse per home visit without qualifications; and £73 for Clinical nurse specialist per hour with patient without (Curtis 2008).

b. Background management during PFS after end of treatment

The model assumes as a proxy for cost after treatment one consultation with a specialist every 2 months (Winstanley 2009). The associated cost is £42.81 per month and it is not assumed to differ by treatment regimen. This is based on a unit cost of £86 for a Clinical Oncology - consultant led: follow-up attendance non admitted face to face visit (National Reference Costs 2007/2008).

c. Background management during progressed disease

When cancer progresses, it is assumed that disease management involves 4 nurse home visit per month, 4 visits with a clinical nurse per month, 2 GP home visit per month, and 2 therapist home visits per month (Winstanley 2009). The associated cost is £564 per month and it is not assumed to differ by treatment regimen. This is based on a unit cost of £23 for Community nurse per home visit without qualifications; £73 for Clinical nurse specialist per hour with patient without qualifications; £50 for General practitioner unit cost including direct care staff costs without qualifications home visit; and £40 for NHS therapist 1 hour home visit without qualifications (Curtis 2008).

4) Adverse event cost

Only those adverse events that occurred in over 3% of patients in E2100 are incorporated into the costing of the paclitaxel and bevacizumab plus paclitaxel model arms. Resource use costs associated with these adverse events are derived from national cost dataset (NHS reference costs 2008/2009) and published literature. As febrile neutropenia occurs in a significant proportion of patients who receive docetaxel (NICE DSU, 2007) the cost of this AE was incorporated into the modelled docetaxel arm. The proportion of patients experiencing 1 or more episode of febrile neutropenia and the mean number of episodes per patient experiencing such an AE were taken from the meta-analysis carried out by the Decision Support Unit as part of the appraisal of erlotinib in TA162 (NICE DSU 2007). It was assumed this rate would not differ significantly between lung and breast cancer patients.

The cost applied to each episode of febrile neutropenia was taken from NHS reference costs 2008/2009. Expert opinion indicated that minimal resources would be required for an episode of Peripheral Sensory Neuropathy and so a cost of £0 was applied in the model.

Table 44. Adverse event costs

Adverse event	Cost per event	Source
Febrile neutropenia	£3803	NHS reference costs 2008/2009 – PA45Z
Hypersensitivity	£274	NHS reference costs 2008/2009 – WA17X
Hypertension	£367	Coon 2008
Infection	£243	NHS reference costs 2008/2009 – WA09W
Peripheral Neuropathy	£0	Expert Opinion

4) End of life cost

Cost from Winstanley 2009 were used to inform cost at end of life. This included the following costs with weighting applied according to the type of health care resource used during the end of life. These figures were inflated from 2006/2007 to 2007/2008 resulting in a final cost of £3,805 applied at the end of life. These cost reflect palliative care cost at the end of life and omit toxicity-related deaths.

Resource use	Cost	Weight
In hospital (2006/07)	£4,706.00	0.4
In Marie Curie hospice (2006/07)	£5,867.00	0.1
At home (2006/07)	£2,428.00	0.5

Table 45 presents the unit cost used in the model for the management of the disease and adverse events.

Table 45 Unit costs for resource use

Item	Unit cost	HRG / service cost	Description
Disease management –related			
CT scan 2 areas w contrast	£130	RA12Z	Computerised Tomography Scan, two areas, with contrast - outpatient
Outpatient visit (consultant) - subsequent visit	£86	800	Clinical Oncology - consultant led: follow-up attendance non admitted face to face
GP contact (surgery visit)	£46	N/A	Curtis 2008, General practitioner unit cost including direct care staff costs without qualifications
GP contact (home visit)	£50	N/A	Curtis 2008, General practitioner unit cost including direct care staff costs without qualifications
Community nurse (home visit)	£23	N/A	Curtis 2008, Community nurse per home visit without qualifications
Clinical nurse specialist (1hour)	£73	N/A	Curtis 2008, Clinical nurse specialist per hour with patient without qualifications
Therapist	£40	N/A	Curtis 2008, NHS therapist 1 hour home visit without qualifications
Hospital pharmacist	£28	N/A	Curtis 2008, Cost per hospital pharamacist without qualifications per hour

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

No resource utilisation data was captured within the E2100 trial therefore it was not possible to align most resource utilisation data with the source of evidence, with the exception of adverse event costs. Assumptions relating to routine patient monitoring and drug administration resources were estimated outside of the trial setting, as described above in Section 7.2.9.2 in more detail.

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

The analysis considers resources for patients on treatment, post-treatment, and post-disease-progression. Please see response in Section 7.2.9.2.

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

National reference costs and PSSRU costs were the preferred means of valuing resources. Where these reference costs did not apply (i.e. hypertension costs) a focused literature search was conducted to obtain applicable UK costs. Drug preparation costs are not captured in the national reference costs, and therefore expert opinion was again sought to approximate the pharmacist time for differing preparations, and this was then costed according to PSSRU.

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

As described in Section 7.2.9.2, the NHS list price of all treatment options will be used.

However, as discussed with NICE during the decision problem meeting (1 Oct 2009), consistent with the gemcitabine appraisal (NICE TA116), a second base case analysis will be provided which will diverge from the NICE reference case due to infomation that BNF list prices for paclitaxel are not representative of typical non-

propietary prices for paclitaxel. Instead, the average PASA price will be utilised following a recommendation at the decision problem meeting. The limitation of using this approach is that a nationally agreed discounted price may not be uniformly available, and therefore the cost-effectiveness results may not be representative of that in all regions of England and Wales and indeed may vary.

A further divergence will be included in this second base case analysis. For bevacizumab, a 10g capping scheme has been in place for several years, available and used widely in the UK private sector and also available to any NHS patient that receives bevacizumab (currently via individual funding requests, etc). The impact of this existing capping programme will be considered.

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

No additional infrastructure would be required for the administration of bevacizumab.

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

Resources were measured and valued in a manner consistent with the reference case. Only costs relating to resources under control of the NHS and PSS were included. Emphasis was placed on identifying resource use where differential effects between the comparator treatments were applicable. Costs were taken from National reference costs 2007/2008, BNF 58, and PSSRU 2008. Only when costs could not be identified from these sources were alternative sources, such as literature review or expert opinion, utilised to inform the model. The assumptions from Winstanley & Murray 2009 were followed where possible.

7.2.9.9 Were resource values indexed to the current price year?

Resource values were indexed to 2008 by using the hospital and community health services inflation indices (Curtis 2008).

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

The monthly resource costs of patients in the PFS health state were assumed equal regardless of treatment arm, with the exception of administration costs and adverse event costs. The monthly resource costs of patients in the progressive health state were assumed equal regardless of 1st line treatment under the basis that taxane choice does not impact subsequent lines of treatment (vinorelbine and capecitabine in general).

7.2.10 Time preferences

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

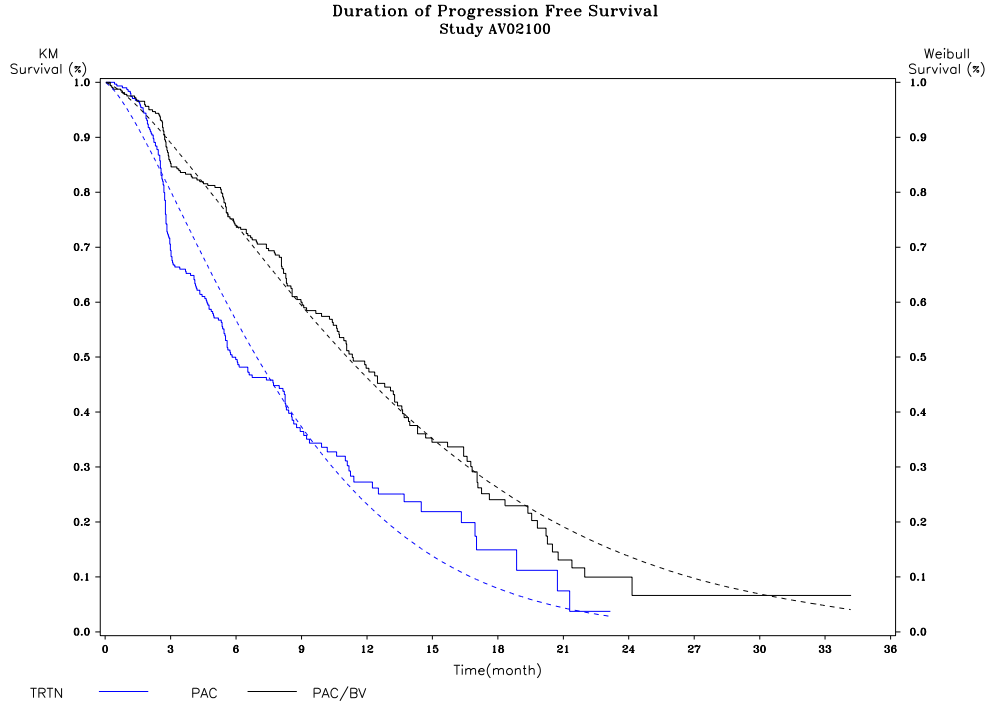
A discount rate of 3.5% was applied to both costs and QALYs in the model.

7.2.11 Sensitivity analysis

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

Selection of the correct parametric function to inform the survival analysis may be considered a source of structural uncertainty and therefore alternative survival functions to the base case Gompertz function for PFS were evaluated. The following figures present the parametric plots of alternative survival function functions (Weibull, Exponential, Log Logistic, Log Normal, and Gamma) overlain onto the KM plots for the PFS.

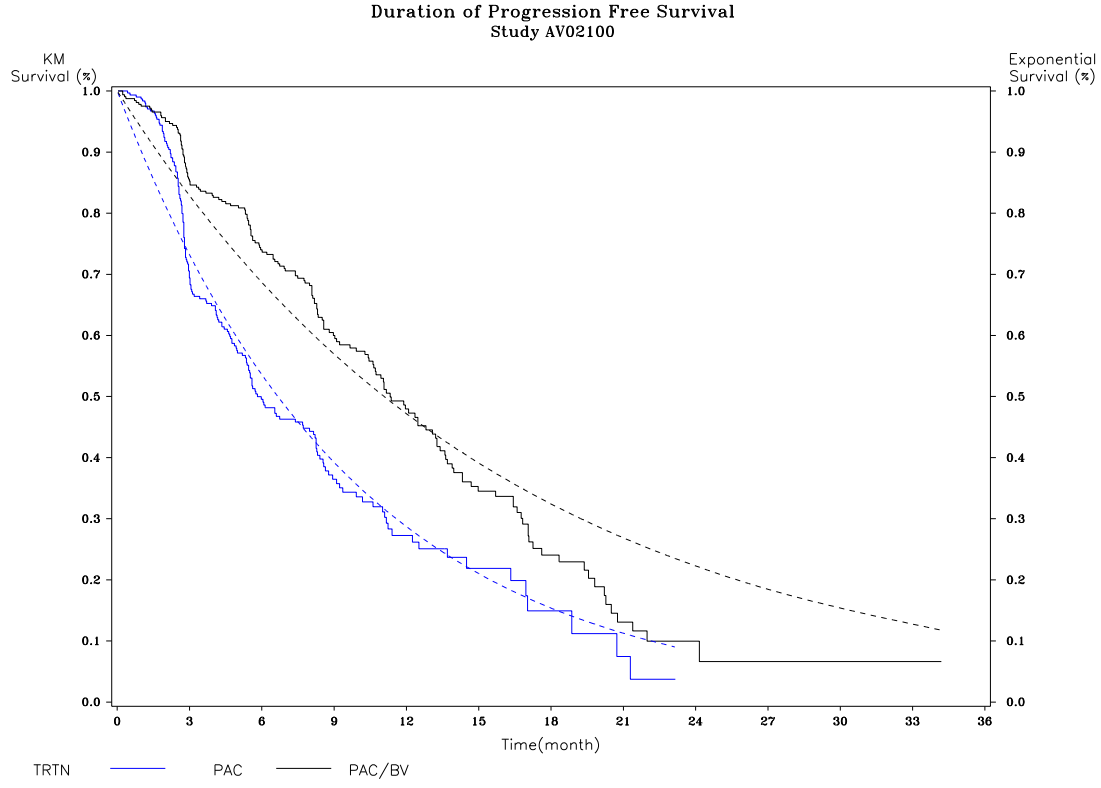
Figure 18. Extrapolated Progression Free Survival curves (Weibull)



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 12OCT2009 16:16

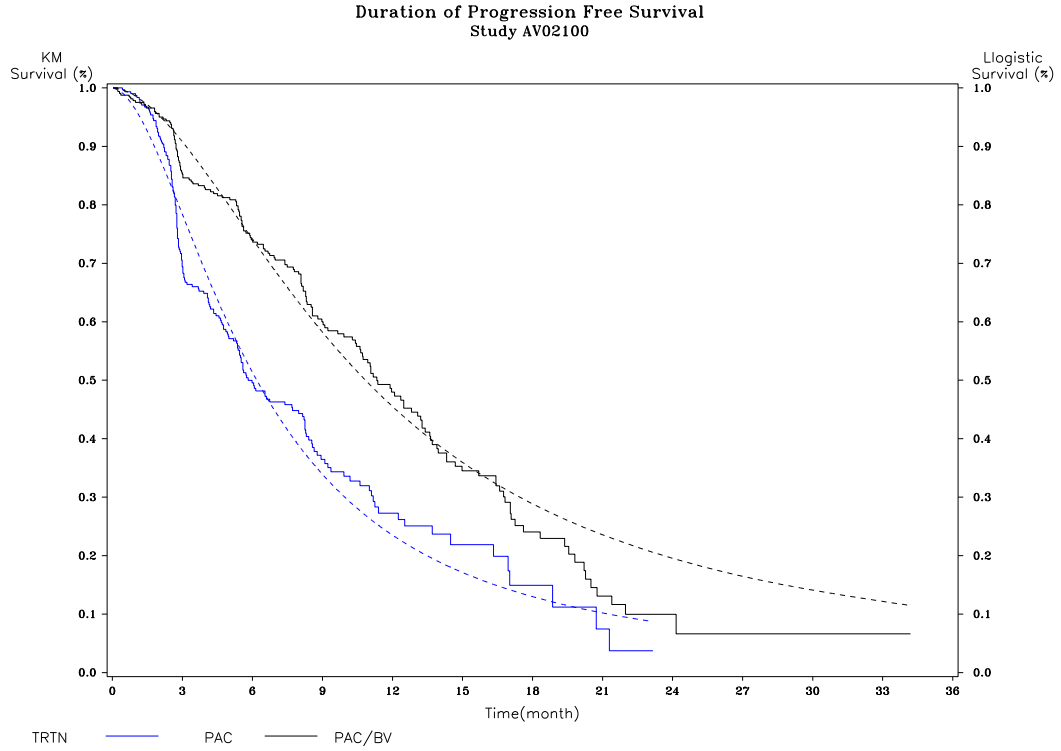
Figure 19. Extrapolated Progression Free Survival curves (Exponential)



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 12OCT2009 16:16

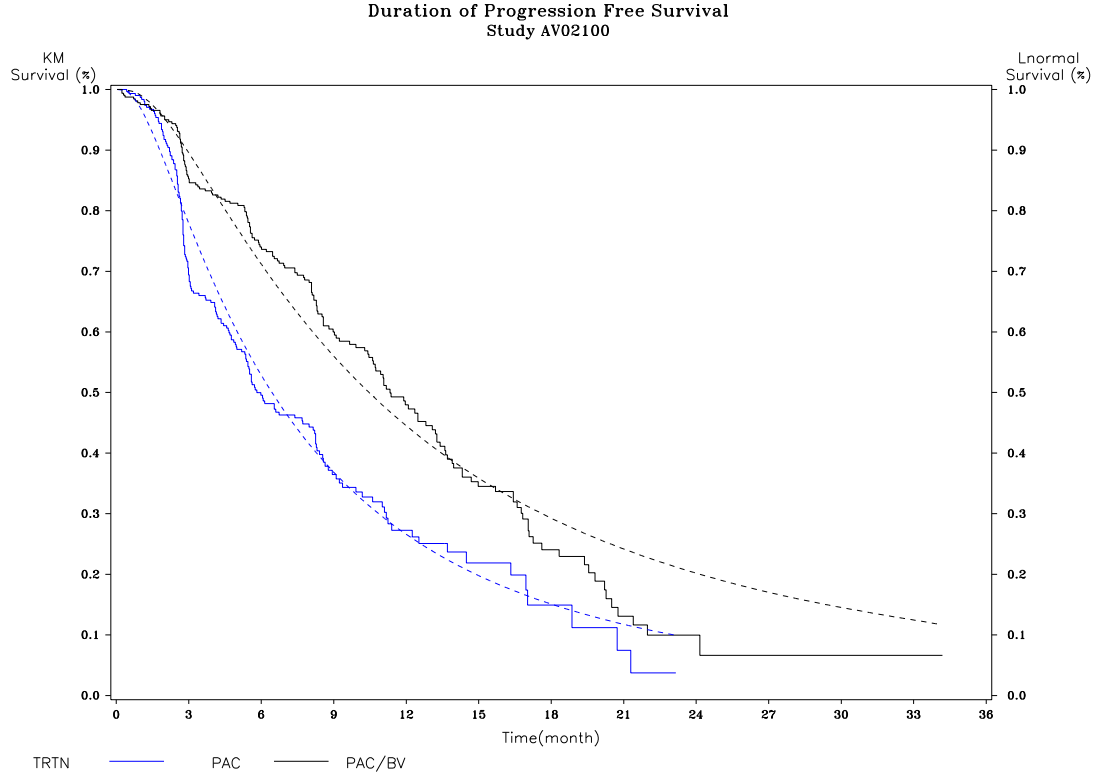
Figure 20. Extrapolated Progression Free Survival curves (Log Logistic)



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 12OCT2009 16:16

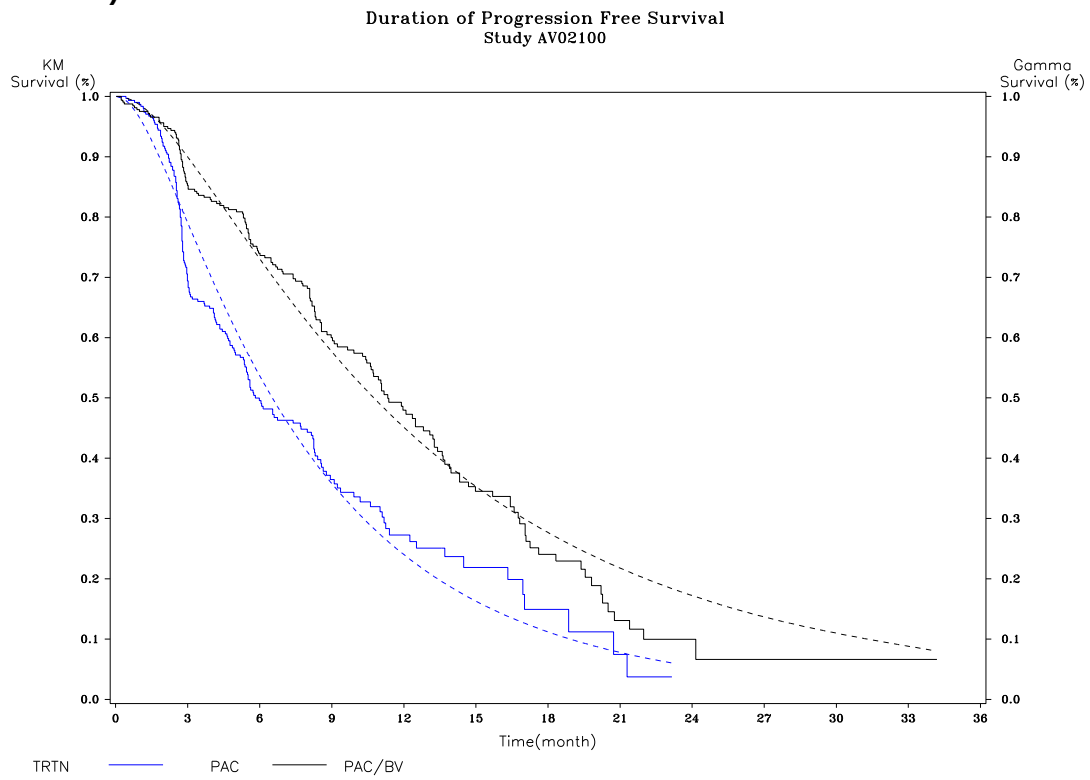
Figure 21. Extrapolated Progression Free Survival curves (Log Normal)



Population: ITT N=722

Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/av02100.pbe/modldth.sas 12OCT2009 16:16

Figure 22. Extrapolated Progression Free Survival curves (Generalized Gamma)



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

1.) Treatment related assumptions

a. Treatment to progression (recommended dosing) for all therapies

The assumption of continuing treatment until progression (as recommended in the SPC for all the comparators in this analysis) was explored in this analysis as opposed to the base case assumption of actual time to off treatment for Bev-Pac and Pac from the clinical trial. This assumption therefore implies that patients do not stop treatment early due to toxicities or any other reasons. However no corresponding changes to efficacy or adverse events are assumed, which are likely to occur as the dose of chemotherapy is increased. Similar to the base case, wastage is included.

b. Patient weight and body surface area

The base case analysis assumed the average patient weight is 70kg and corresponds to a body surface area of 1.7m^2. This is consistent with the manufacturer submission for Herceptin in mBC. Few other economic analyses in the literature required an estimate of both kilograms and BSA in order to perform their analyses. There are several BSA values assumed in the literature ranging from 1.66 m^2 (Hutton 1996, Brown 1998), to 1.7 m^2 (Hercetpin mBC TA34 and Xeloda mBC TA62), 1.75 m^2 (Brown 2001 and Winstanley 2009), to 1.8 m^2 (gemcitabine mBC TA116). Due to any lack of consistency in the appropriate weights to consider, we have arbitary chosen to consider the impact on the cost-effectiveness if patient weights/body surface area were to vary as follows

- 60 kilograms corresponding to 1.6 m^2
- 80 kilograms corresponding to 1.8 m^2

As always, wastage is included in this analysis.

2.) Utility values

Additional scenario analyses were considered for the model utility scores.

a. Treatment-specific response rate-weighted utility scores

In the sensitivity analysis, we consider the impact of different response rates by treatment arm on quality of life. For the PFS health state, the utility of the cohort is weighted for the proportion of individuals that respond to treatment at each arm (Table 46).

Table 46. Best clinical response: responders and stable disease in E2100

Treatment Arm	Partial response N (% of those not progressing)	Stable disease N (% of those not progressing)	Total
paclitaxel	54 (33.75%)	106 (66.25%)	160
bevacizumab + paclitaxel	114 (59.69%)	77 (40.31%)	191

For docetaxel and gemcitabine + paclitaxel, we attempted to account for differences in response rates to inform the PFS utility. Because response rate as a proportion of those in PFS is not available for the other comparators, this proportion was calculated by the relative difference in proportion of response compared to paclitaxel weekly in E2100 (33.75%). For instance, to determine the docetaxel responders as a proportion of those in PFS, 33.75% from the E2100 paclitaxel arm was multiplied by 29%/42% to adjust to a paclitaxel 3-weekly responders as a proportion of those in PFS (Seidman 2008) which was then multiplied by 32%/25% to adjust to a docetaxel responders as a proportion of those in PFS (Jones 2005). A similar exercise was applied to gemcitabine + paclitaxel.

Table 47. Response rates in trials used to inform indirect comparisons

Response Rates	Treatment arm 1		Treatment arm 2	
Seidman 2008	29%	Q3W paclitaxel	42%	QW paclitaxel
Albain 2008	26.2%	Q3W paclitaxel	41.4%	GemPac
Jones 2005	25%	Q3W paclitaxel	32%	docetaxel

Table 48. Calculation of PFS health state utility values for indirect comparisons

Indirect treatment comparison	% of responders	% stable disease	PFS utility value
docetaxel	29.83%	70.17%	0.698
gemcitabine + paclitaxel	36.82%	63.18%	0.709

Table 49 Utility scores applied to the model sensitivity analysis #1 (after adjustment for response)

Health state	Bev-Pac	Pac	Doc	Gem-Pac
PFS	0.7455	0.704	0.698	0.709
PD	0.45	0.45	0.45	0.45

b. Lloyd 2006 utility scores

The second scenario uses utility scores from Lloyd et al. (2006). The utility scores are estimated based on a 55.5 year old patient (average age of patients in E2100). The disutility of adverse events is assumed to be the same between febrile neutropenia and peripheral neuropathy. The disutility of the event is derived by the

difference between the health state utility without toxicity and that of the health state with febrile neutropenia (0.-15). Table 50 presents the utility scores from Lloyd et al, 2006. Similarly to the above sensitivity analysis, treatment-specific PFS health state is weighted for the proportion of responders and the incidence of adverse events in each arm.

Table 50 Utility scores considered in scenario #2

Health state	Utility score	Reference
Response –no toxicity	0.851	Lloyd 2006
Stable disease –no toxicity	0.792	Lloyd 2006
Progressive disease	0.547	Lloyd 2006
Disutility from febrile neutropenia	-0.15	Lloyd 2006derived from stable disease health state applied in month 1 only
Disutility from peripheral sensory neuropathy	-0.15	Assumed similar to febrile neutropenia

Table 51 Utility scores applied to the model sensitivity analysis #2 (after adjustment for response)

Health state	Bev-Pac	Pac	Doc	Gem-Pac
PFS	0.827	0.812	0.809	0.814
PD	0.547	0.547	0.547	0.547

3.) Resource utilisation costs

Two alternative scenarios was considered for the cost of resource utilisation.

a. Supportive care treatment costs

Supportive care costs were increased and decreased by 50% in this sensitivity analysis.

b. Expert opinion of PFS cost; published literature on Progressed cost

In the second scenario the model assumes that disease management before disease progression involves only one CT scan and one consultant visit every three months. Moreover, the second scenario uses a value from the published literature for the cost of progressive disease (£771) as well as the cost at end of life (£1,503) (inflated to 2008 prices) (Remak et al. 2004).

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

PSA was undertaken. An assumption of 1,000 samples was used in order to achieve reasonably tight distributions around the mean estimate. Lower sample numbers result in very wide and flat distributions, which were deemed to be meaningless. The table below summarises the assumptions relating to distributions and ranges of each parameter included within the PSA analysis. Distributions are applied around the following parameters to reflect parameter uncertainty in the model:

- **Parameter estimates for the parametric (e.g. Gompertz) PFS functions**

- **Monthly probability of death** (applicable to the progressed health state): the probability of moving to the death state was assumed to originate from an exponential function and thus is calculated as the inverse of the restricted means from the Kaplan-Meier based on last observed time . This was varied by the Beta Pert function.

- **Utilities for PFS and progression**: The parameters for the distributions used for the probabilistic sensitivity analysis are calculated as follows (beta (utility value *1000, (1-utility value) *1000).

- **Monthly supportive care costs** in the PFS health state overall, in the PFS health state after therapy, and in the progressed health state. Values were varied by means of a Beta Pert function within an assumed range of 50% of the base case.

- **Adverse event costs** associated with events occurring during treatment and febrile neutropenia. Values were varied by means of a Beta Pert function within an assumed range of 20% of the base case.

- **Drug administration costs** Values were varied by means of a Beta Pert function within the lower and upper quartile for "Deliver more complex Parenteral Chemotherapy at first attendance" (from reference costs 2006/07).

- **End of life costs**. Values were varied by an assumed range of 20% of the base case.

Table 52. PSA values for monthly supportive care costs and resource utilisation events

Cost	Base case	Minimum	Maximum
PFS	£165.00	£115.50	£214.50
PFS post-therapy	£42.81	£29.97	£55.66
Progressed	£564.00	£394.80	£733.20
Administration - Deliver more complex Parenteral Chemotherapy	£95.75	£237.00	£309.50
End of life costs	£3,804.59	£3043.67	£4,565
Febrile Neutopenia	£3,803	£3,042	£4,564
Hypersensitivity	£274	£219	£329
Hypertension	£230	£184	£276
Infection	£243	£194	£292
Febrile Neutopenia	£3803	£3042	£4564

For a more detailed description of the beta-pert distribution please see: http://www.decisioneering.com/support/risktips/risktip-3.html.

7.2.12 Statistical analysis

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

Please see Section 7.2.6.8 above.

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

The best-fit to the PFS data in the E2100 study was the Gompertz function. PFS is modelled under the assumption of proportional hazard (PH) using the Gompertz function whose hazard function is non constant over time. Post progression to death assumes a constant hazard of death however the model assesses uncertainty with this estimate with probabilitistic sensitivity analysis by sampling from a normal distribution with mean and variance (Table 35) described above (estimating survival of progressed patients).

7.2.13 Validity

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

The internal validation and debugging of the model was performed by Outcomes International, an independent consultant company specialized in the development and validation of decision analytic models used for health economic analyses. The following validation procedures were performed:

- Check of completeness of reported results (health outcomes, economic outcomes) as compared to other published economic evaluations targeting the same indication
- Execution of selected extreme tests to check the plausibility of model outcomes. Extreme testing was applied to the following parameters: treatment efficacy, adverse event costs, cost of study drugs and administration, discount rates, and health utilities

7.3 Results

7.3.1 Base-case analysis

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

Cost-effectiveness of bevacizumab in combination with paclitaxel

Two base case analyses are provided:

(1) The NICE reference case for the treatment of bevacizumab and paclitaxel

(2) Using the paclitaxel PASA price and the 10g cap for bevacizumab (as described in Section 7.2.9.6)

Costs

Table 53 indicates that bevacizumab given in combination with paclitaxel is associated with an additional average per-patient costs of £30,469, £31,416, and £27,358 over the analysed patients' lifetime period (a maximum of 10 years) when compared to pac, doc, and gem-pac. These results are based on NHS list prices.

Table 53: Total average per-patient cost for each treatment groups over a lifetime period of 10 years (deterministic analysis) – NHS list price

Cost component (£)	Bev-Pac	Pac	Doc	Gem-Pac
Mean cost of PFS	**£41,935**	**£11,393**	**£10,446**	**£14,503**
Costs of bevacizumab	£25,929	£0	£0	£0
Administration costs of bevacizumab	£110	£0	£0	£0
Cost of paclitaxel	£7,720	£5,650	£0	£4,185
Administration costs of paclitaxel	£5,782	£4,232	£0	£2,073
Costs of docetaxel or gemcitabine			£6,723	£4,987
Administration costs of docetaxel or gemcitabine			£1,867	£1,748
Adverse event costs	£108	£6	£332	£6
Cost of supportive care in PFS	£2,286	£1,504	£1,524	£1,504
Mean cost of Progression	**£14,538**	**£14,612**	**£14,612**	**£14,612**
Cost of supportive care in Progression	£11,109	£11,131	£11,131	£11,131
End of life costs	£3,429	£3,481	£3,481	£3,481
Mean Total Cost	**£56,473**	**£26,004**	**£25,057**	**£29,115**
Incremental Cost		**£30,469**	**£31,416**	**£27,358**

Table 54 indicates that bevacizumab given in combination £19,997, £15,769, and £15,545 over the analysed patients' lifetime period (a maximum of 10 years) when compared to pac, doc, and gem-pac. These results are based on the PASA price for paclitaxel and the 10 gram capping programme available for bevacizumab in the UK.

Table 54: Total average per-patient cost for each treatment groups over a lifetime period of 10 years (deterministic analysis) – PASA paclitaxel price + 10g cap

Cost component (£)	Bev-Pac	Pac	Doc	Gem-Pac
Mean cost of PFS	**£26,288**	**£6,218**	**£10,446**	**£10,670**
Costs of bevacizumab	£17,352	£0	£0	£0
Administration costs of bevacizumab	£110	£0	£0	£0
Cost of paclitaxel	£649	£475	£0	£352
Administration costs of paclitaxel	£5,782	£4,232	£0	£2,073
Costs of docetaxel or gemcitabine			£6,723	£4,987
Administration costs of docetaxel or gemcitabine			£1,867	£1,748
Adverse event costs	£108	£6	£332	£6
Cost of supportive care in PFS	£2,286	£1,504	£1,524	£1,504
Mean cost of Progression	**£14,538**	**£14,612**	**£14,612**	**£14,612**
Cost of supportive care in Progression	£11,109	£11,131	£11,131	£11,131
End of life costs	£3,429	£3,481	£3,481	£3,481
Mean Total Cost	**£40,826**	**£20,829**	**£25,057**	**£25,281**
Incremental Cost		**£19,997**	**£15,769**	**£15,545**

Life Years and Quality-Adjusted Life Years

Table 55 shows that the combination of Bev-Pac results in a mean gain of 0.352 life years when compared to all 3 regimens and 0.259, 0.273, and 0.259 quality-adjusted life years (QALYs) when compared Pac, Doc, and Gem-Pac over the analysed lifetime period of 10 years. The difference in QALY values attributed to each comparator despite equal life year gains is due to the different adverse event profiles associated with each comparator (particularly the role of febrile neutropenia in patients receiving docetaxel).

The incremental QALYs produced by bevacizumab plus paclitaxel over the comparators are largely due to a longer stay in the health state of progression-free survival (PFS) for the patients assigned Bev-Pac than that observed for patients assigned Pac, Doc, or Gem-Pac. This is further illustrated in the figure below where patients in the Pac arm progress quicker and have a marginally shorter time to death than Bev-Pac patients. The model estimates 0.355 additional life years in PFS for the

Bev-Pac arm compared to the Pac arm which is model compared to the difference in the median PFS duration observed in the E2100 trial of 0.46 years (5.5 months).

Table 55: Total mean QALYs per patient for the compared treatment groups over a lifetime period of 10 years (deterministic analysis)

Outcome measure	Bev-Pac	Pac	Doc	Gem-Pac
Mean Life Years (yrs)	2.682	2.330	2.330	2.330
Mean Life Years in PFS (yrs)	1.041	0.686	0.686	0.686
Mean life Years in Progression (yrs)	1.641	1.645	1.645	1.645
Incremental Life Years		**0.352**	**0.352**	**0.352**
Mean QALYs	1.498	1.239	1.225	1.239
Mean QALY in PFS	0.759	0.499	0.485	0.499
Mean QALY in Progression	0.739	0.740	0.740	0.740
Incremental QALYs		**0.259**	**0.273**	**0.259**

Incremental Cost-Utility Ratio

Based on the assumptions used for the core model analysis, a cost per QALY of £117,803, £115,059, and £105,777 for Bev-Pac therapy relative to Pac, Doc, and Gem-Pac therapy was calculated (Table 56). These results are based on NHS list prices.

Table 56: Cost per life year/cost per QALY gained ratios for Bev-Pac over a lifetime period of 10 years (deterministic analysis) – NHS list price

Cost-utility results	Bev-Pac	Pac	Doc	Gem-Pac
Mean Life Years (yrs)	2.682	2.330	2.330	2.330
Mean QALYs	1.498	1.239	1.225	1.239
Mean Total Cost	£56,473	£26,004	£25,057	£29,115
Incremental Life Years		*0.352*	*0.352*	*0.352*
Incremental QALYs		*0.259*	*0.273*	*0.259*
Incremental Cost		*£30,469*	*£31,416*	*£27,358*
Cost per Life Year Gained		**£86,572**	**£89,263**	**£77,734**
Cost per QALY Gained		**£117,803**	**£115,059**	**£105,777**

Based on the assumptions used for the core model analysis, a cost per QALY of £77,314, £57,753 and £60,101 for Bev-Pac therapy relative to Pac, Doc, and Gem-Pac therapy was calculated (Table 57). These results are based on the PASA price

for paclitaxel and the 10 gram capping programme available for bevacizumab in the UK.

Table 57: Cost per life year/cost per QALY gained ratios for Bev-Pac over a lifetime period of 15 years (deterministic analysis) – real-world prices

Cost-utility results	Bev-Pac	Pac	Doc	Gem-Pac
Mean Life Years (yrs)	2.682	2.330	2.330	2.330
Mean QALYs	1.498	1.239	1.225	1.239
Mean Total Cost	£40,826	£20,829	£25,057	£25,281
Incremental Life Years		*0.352*	*0.352*	*0.352*
Incremental QALYs		*0.259*	*0.273*	*0.259*
Incremental Cost		*£19,997*	*£15,769*	*£15,545*
Cost per Life Year Gained		**£56,818**	**£44,805**	**£44,168**
Cost per QALY Gained		**£77,314**	**£57,753**	**£60,101**

Cost-effectiveness of bevacizumab in combination with docetaxel

The base case results provided above suggest that bevacizumab in combination with paclitaxel has an ICER greater than £50,000.. This is despite a median doubling in progression-free survival and also considering the combination of bevacizumab with a relatively inexpensive taxane (paclitaxel at PASA price) compared to a substantially more expensive taxane (docetaxel). It can therefore be inferred that bevacizumab in combination with docetaxel (the expensive taxane), which is associated with a similar level of treatment benefit, is highly unlikely to provide a more cost-effective outcome than the analysis presented in this submission due to its more expensive costs. It is therefore clear, without the need of a full economic analysis, that bevacizumab in combination with docetaxel is not cost-effective by UK standards.

7.3.2 Subgroup analysis

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

No sub-group analysis was performed for the reasons outlined in Section 7.2.2.2.

7.3.3 Sensitivity analyses

7.3.3.1 What were the main findings of the sensitivity analyses?

The following table provides the incremental cost-effectiveness results for a selection of one-way sensitivity analyses. The following tornado diagram ranks these scenarios in terms of impact on the ICER. Sensitivity analysis was performed only on the second base case scenario where the PASA price of paclitaxel and the 10g bevacizumab cap are incorporated.

Table 58. One-way sensitivity analyses

Sensitivity analyses: Bev/Pac compared to	Pac	Doc	Gem/Pac
Base case	£77,314	£57,753	£60,101
Weibull function	£70,662	£52,128	£54,951
Exponential function	£57,838	£44,766	£45,055
Log logistic function	£53,492	£40,448	£41,660
Log normal function	£58,969	£44,363	£45,919
Generalized Gamma function	£62,591	£46,743	£48,716
First line treatment administered until progression	£97,308	£60,832	£67,833
Utilities: Weighted by response rates (Cooper 2003)	£68,343	£50,655	£53,746
Utilities: Weighted by response rates (Lloyd 2006)	£65,977	£50,066	£51,500
Monthy supportive care cost: alternative values (Remak 2004)	£74,728	£55,376	£57,515
Monthly supportive care cost decrease by 50%	£75,844	£56,397	£58,631
Monthly supportive care cost increase by 50%	£78,784	£59,109	£61,571
Patient weight = 60kg; 1.6 m2	£67,350	£48,023	£49,921
Patient weight = 80kg; 1.8 m2	£85,289	£65,307	£66,233

Figure 23. Tornado diagram of one-way sensitivity analyses (paclitaxel comparison)

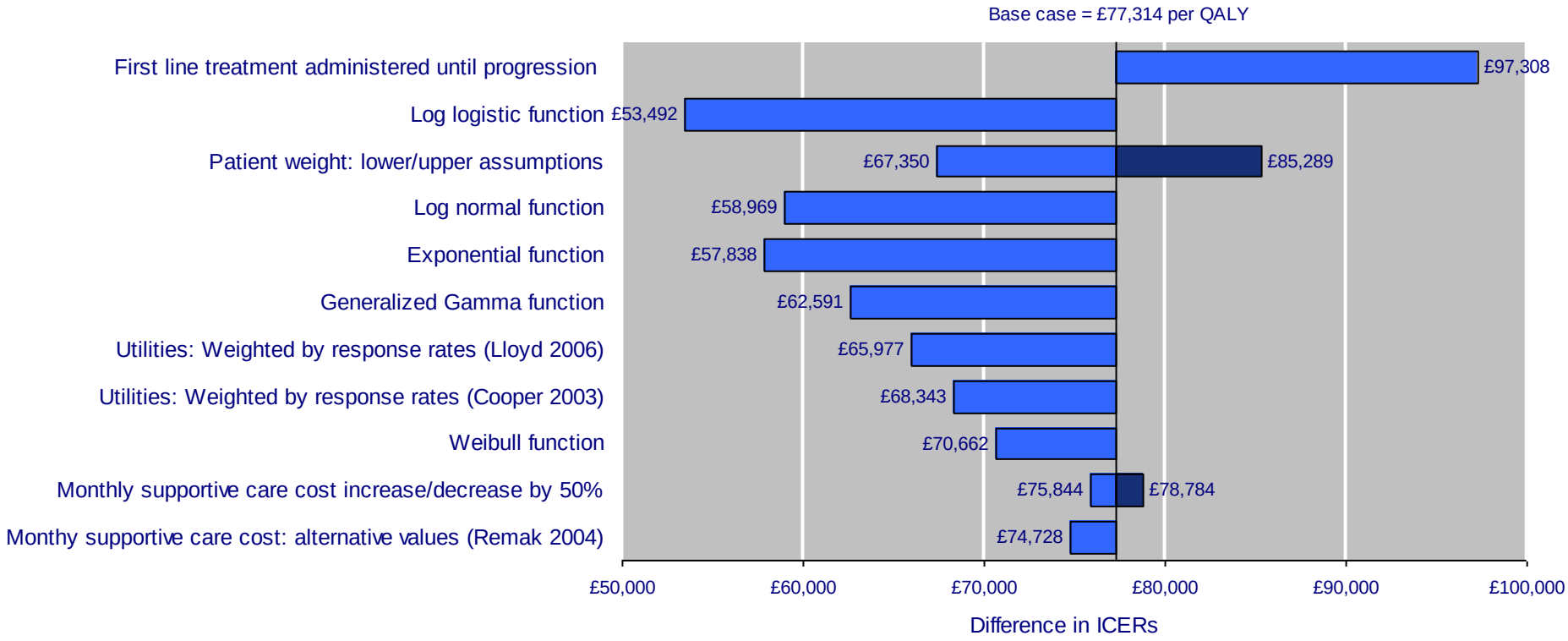


Figure 24. Tornado diagram of one-way sensitivity analyses (docetaxel comparison)

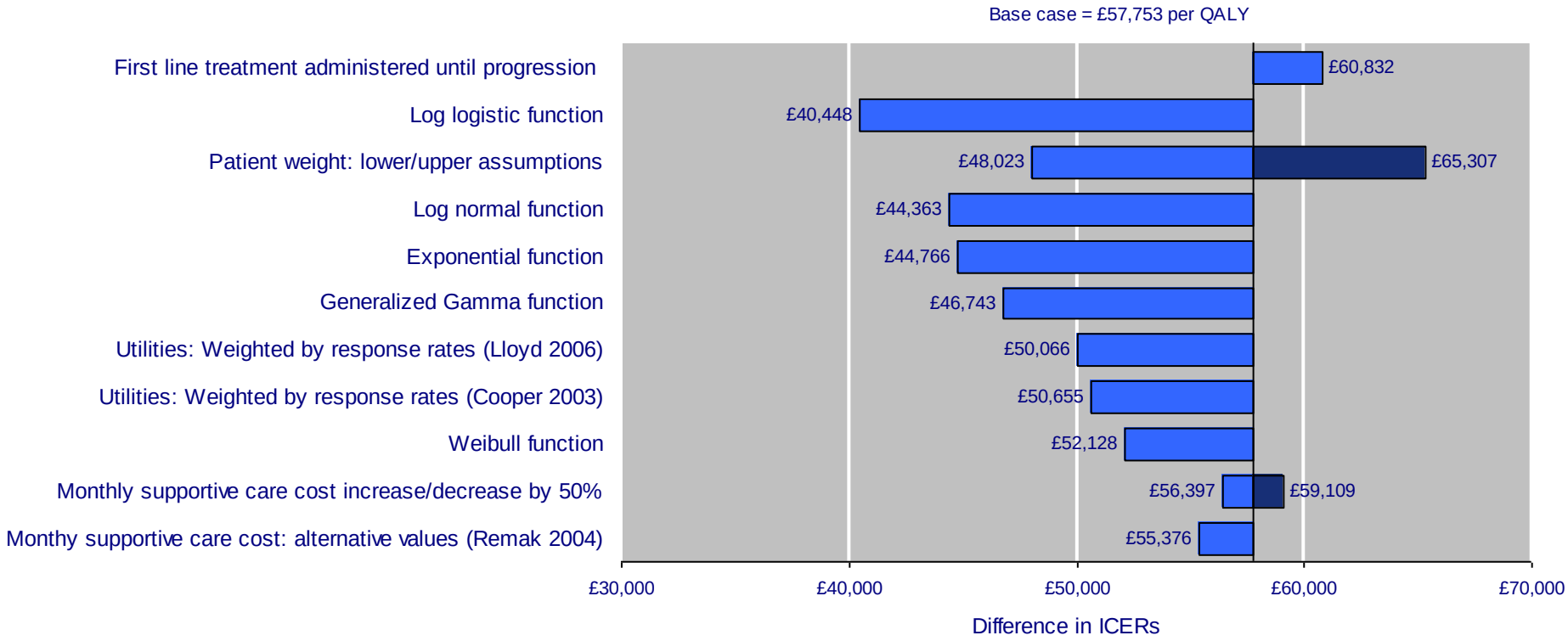
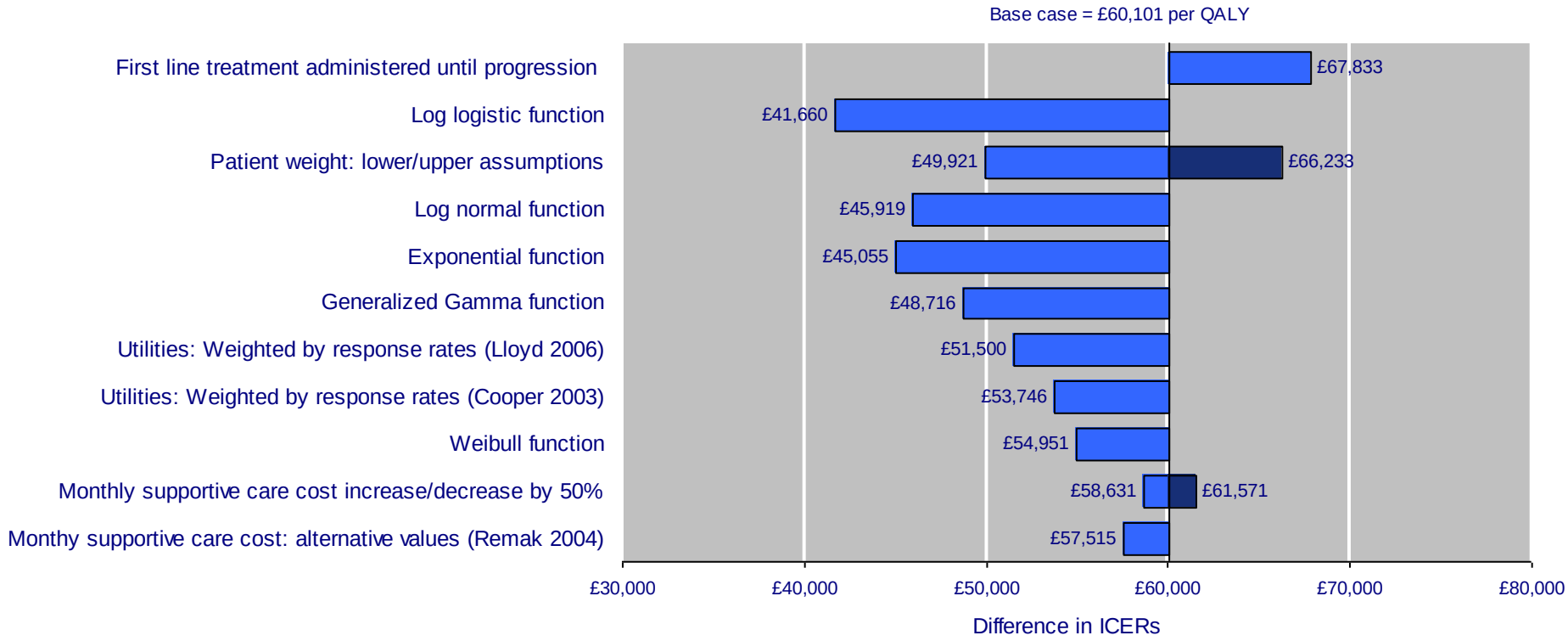


Figure 25. Tornado diagram of one-way sensitivity analyses (gemcitabine + paclitaxel comparison)



Probabilistic sensitivity analyses

When using a sufficiently high number of Monte Carlo simulations - as example 1,000 iterations - the model produces probabilistic health and economic outcomes that are comparable to that obtained from the deterministic analysis. Below are the mean cost and outcome results from 1,000 runs.

Table 59. Mean Cost Effectiveness results (1000 runs)

Sensitivity analyses: Bev/Pac compared to	Pac	Doc	Gem/Pac
Cost per Life Year Gained (£)	**£56,248**	**£45,323**	**£38,628**
Cost per QALY Gained (£)	**£76,571**	**£58,645**	**£51,450**

Scatter plots

The cost-effectiveness plane in the example presented below (assumption: 1,000 patients running individually through the model) shows the distribution of incremental cost per QALY ratios in relation to an assumed willingness to pay (WTP) ceiling ratio of £30,000 per QALY.

Figure 26: Scatter plot of cost per QALY for paclitaxel comparison

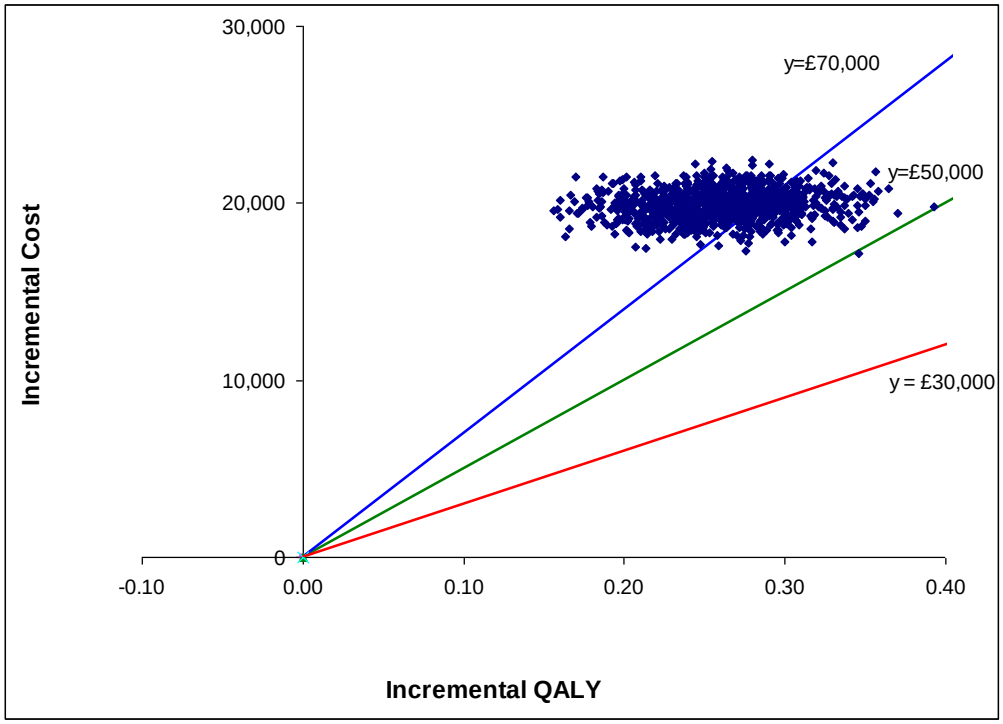


Figure 27: Scatter plot of cost per QALY for docetaxel comparison

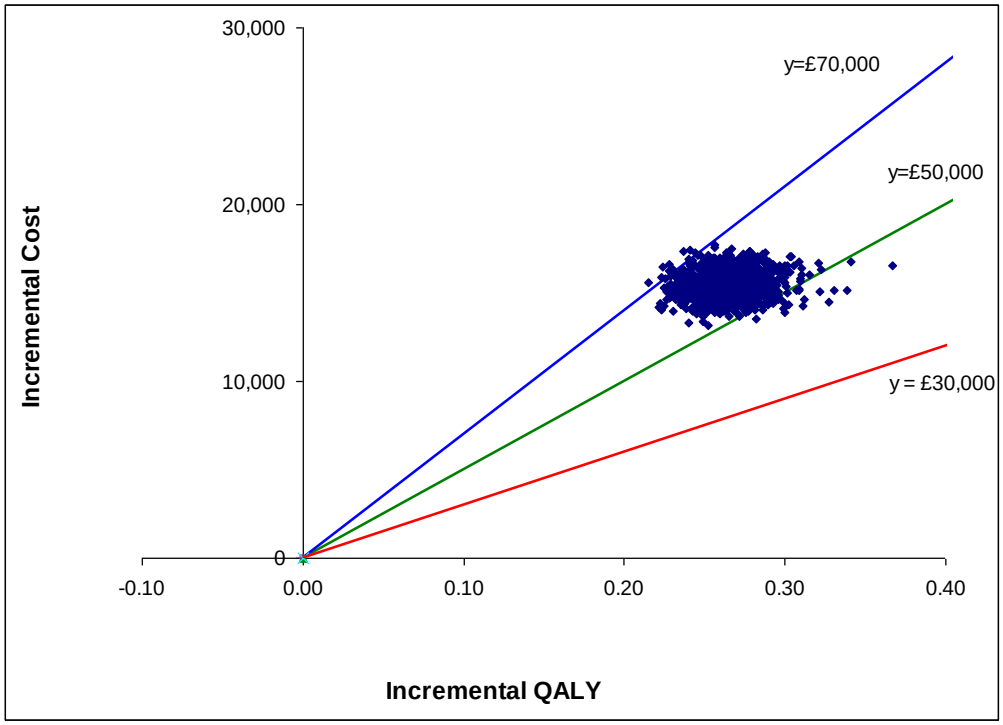
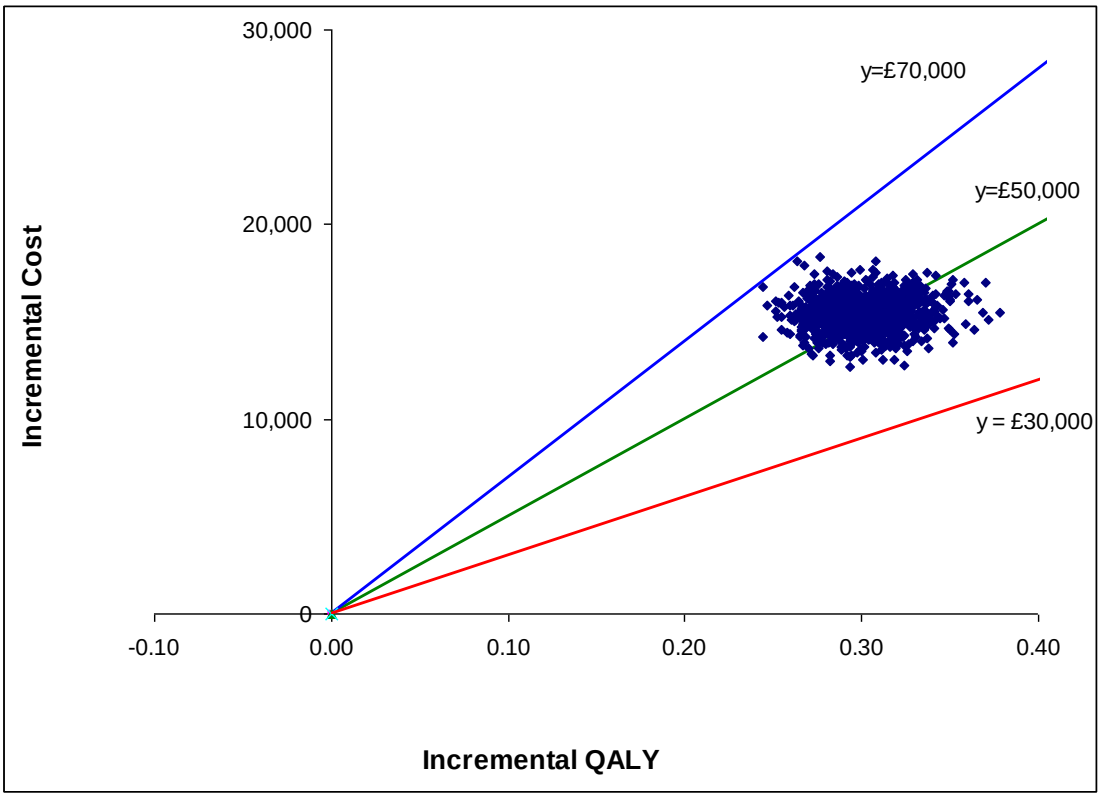


Figure 28: Scatter plot of cost per QALY for gemcitabine+paclitaxel comparison



Cost-effectiveness acceptability curve (CEAC)

The CEAC graph shows the likelihood of the Bev-Pac treatment being cost-effective at different WTP per QALY thresholds. The probability of not surpassing the £30,000 threshold is 0% against all comparators.

Figure 29: Cost-effectiveness acceptability curve compared to paclitaxel

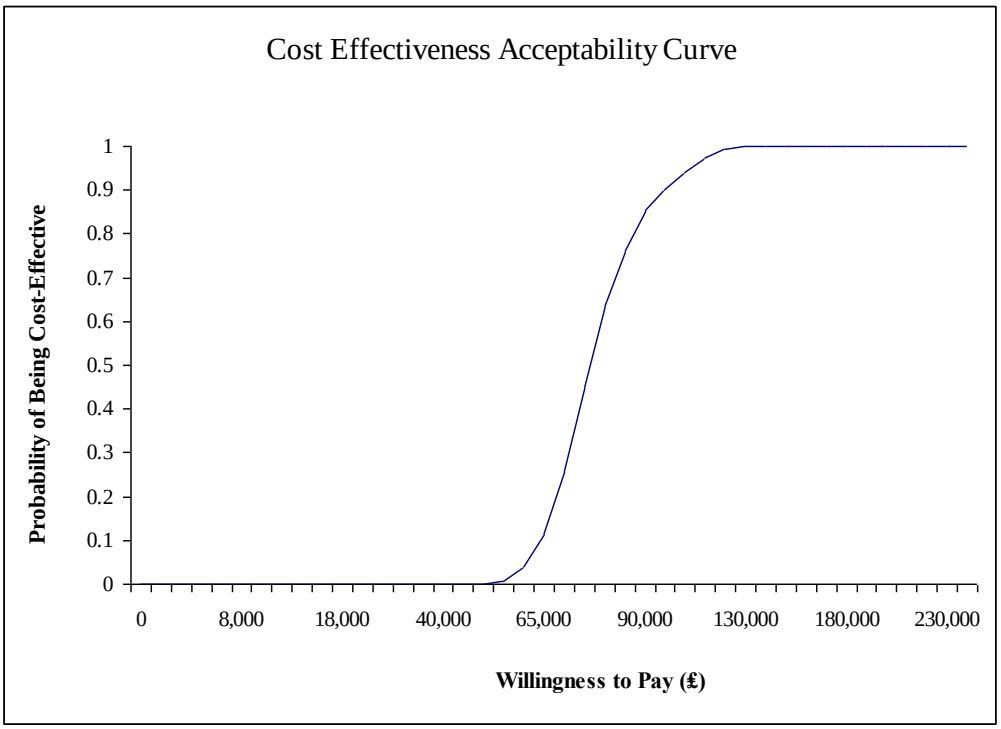


Figure 30: Cost-effectiveness acceptability curve compared to docetaxel

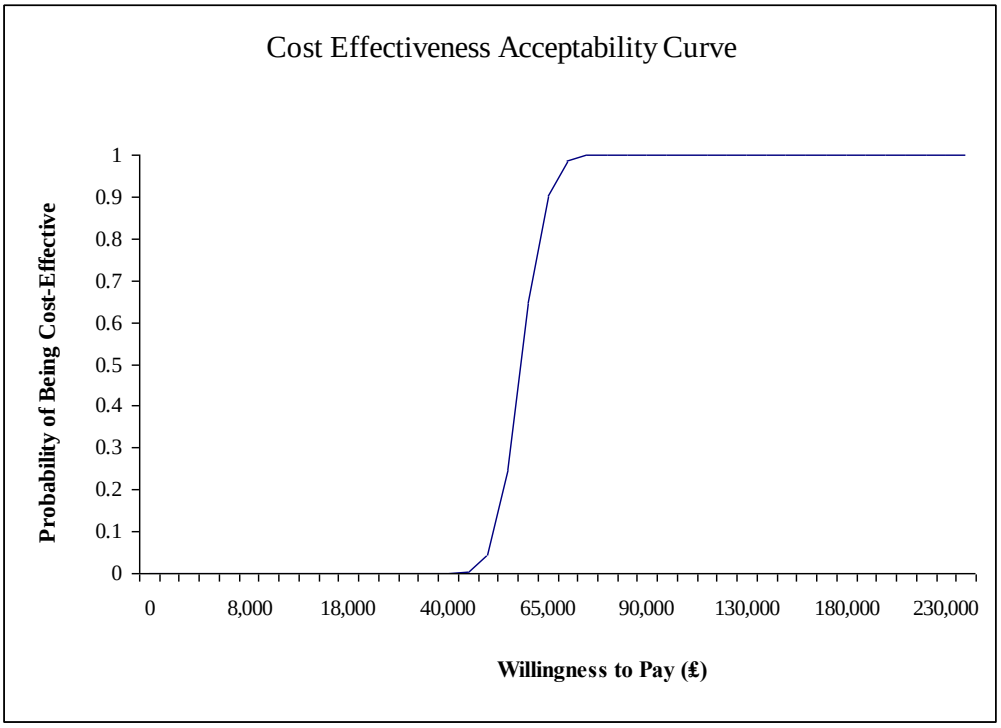
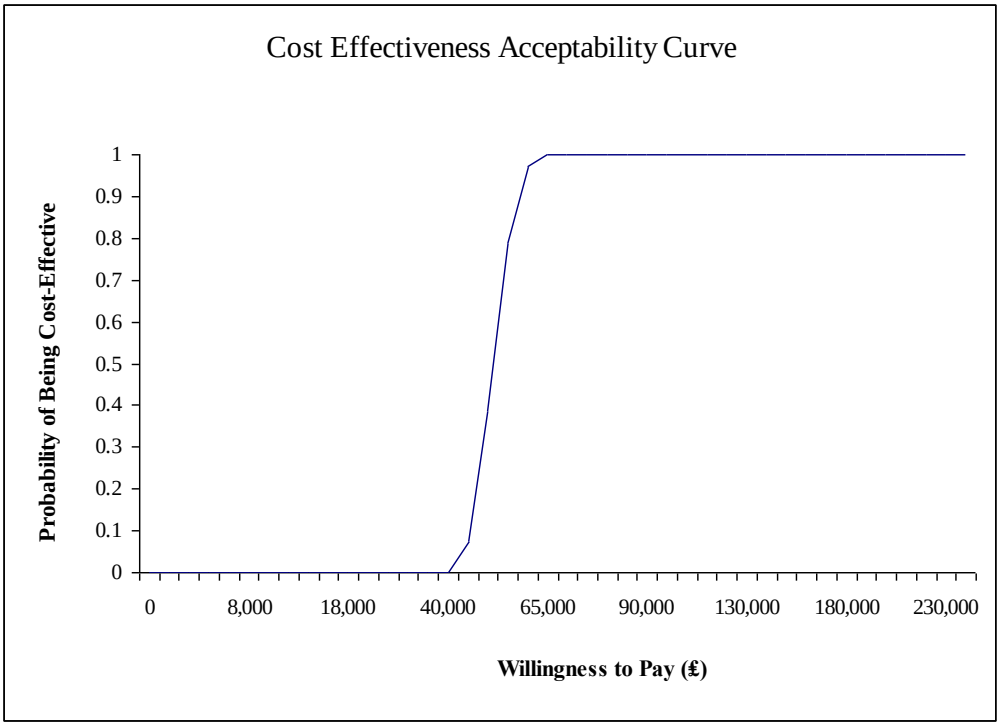


Figure 31: Cost-effectiveness acceptability curve compared to gemcitabine/paclitaxel



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

Utilising different parametric functions for survival extrapolation and alternative assumptions on treatment duration had the largest impact on the ICERs. Supportive care cost and different assumptions to utilitiy scores had a smaller impact on the ICERs.

7.3.4 Interpretation of economic evidence

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

No previous economic evaluation of bevacizumab in 1st line mBC have been published from a UK perspective.

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

The economic evaluation was based upon its licensed indication and aligned with the baseline characteristics of those patients included within the E2100 study. There is no evidence to suggest that this is not a reasonably representative sample of the likely recipients of bevacizumab in England and Wales.

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

Strengths

a) The incremental clinical effects of Bev-Pac compared to Bev are based upon a large randomised head to head controlled trial demonstrating a significant treatment effect of adding bevacizumab to paclitaxel. Consequently the certainty of the treatment effect of bevacizumab and the subsequent incremental clinical advantages of Bev-Pac compared to Pac is strong.

b) The extrapolation of the primary endpoint, PFS, from the E2100 study is based on a relatively long follow up period of 4.5 years

c) Where possible, the cost and utilities assumptions were taken from the recent economic evaluation which informed the NICE clinical guidelines (CG 81)

d) Several types of uncertainties have been evaluated in both one-way and probabilistic sensitivity analysis. The resultant ICER has been demonstrated to be very stable to wide variations in model parameters.

Weaknesses

a) The existing limited evidence base makes formal indirect comparisons between bevacizumab in combination with paclitaxel versus docetaxel (UK standard of care) a challenge. Therefore a simplying assumption (i.e. a taxane class effect for paclitaxel weekly compared to docetaxel 3-weekly) was necessary in order to make this comparison.

b) The aggregated nature of the progressed health state may appear an over-simplification of the natural disease progression of a mBC patients. However as the sensitivity analysis illustrates, despite a wide variation in the assumed value of these particular parameters (cost and utility of the progressed health state) the ICER remains relatively insensitive to this issue. The effect of re-treatment can still be argued to be captured based upon the types of costs included and the risk of death utilised for this health state.

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

a) A direct RCT comparison of paclitaxel weekly to docetaxel 3-weekly using standard UK doses and duration of treatment

b) An improved understanding of the impact of bevacizumab on quality of lfie whilst in PFS, particularly in comparison to UK standard of care, docetaxel.

c) A more detailed understanding of the proportion of time a mBC patient spends with and without active disease, following relapse of their 1st line of treatment.

8 Assessment of factors relevant to the NHS and other parties

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

The below budget impact analysis is founded on the assumption that in this appraisal only bevacizumab/paclitaxel combination therapy will be approved by NICE in the first line treatment of HER2 negative metastatic breast cancer.

If it is assumed that the uptake of 1st line bevacizumab and paclitaxel combination therapy in those patients suitable to receive such a combination for metastatic breast cancer (i.e those equivalent to the ITT population of E2100) is 4% in 2010, 25% in 2011 and 45% in 2012 the estimated budget impact of the addition of bevacizumab to the current 1st line taxane based treatment regimens for the treatment of HER2 negative metastatic breast cancer patients is £2.60. million in 2010, £13.23 million in 2011 and £21.46 million in 2012.

The above are inclusive of administration costs and assume the use of a 10g bevacizumab capping scheme (as is already available and widely used in the UK private sector).

8.2 What number of patients were assumed to be eligible? How was this figure derived?

Bevacizumab is indicated for the first-line treatment of patients with HER2 negative metastatic breast cancer in combination with paclitaxel or docetaxel. The estimated numbers of patients eligible for treatment under this indication were calculated individually for both England and Wales and then combined to estimate the total number of eligible patients.

England

The breast cancer incidence rate in England in 2006 was 0.0754% (Cancer Research UK, February 2006). For the purposes of this evaluation it is assumed that this rate is representative of the incidence rate in 2010, 2011 and 2012.

The population of England is predicted to be 52,706,471 in 2010, 53,113,335 in 2011 and 53,514,508 in 2012 (GAD, 2006-based principal projections). A breast cancer incidence rate of 0.0754% will result in 39,741 new breast cancer patients in 2010, 40,047 in 2011 and 40,350 in 2012.

Approximately 26% of all individuals presenting with breast cancer have a metastatic form of the disease (Cancer Research UK, February 2006) (estimated no. of new metastatic breast cancer patients in England; 2010: 10,333, 2011: 10,412, 2012:10,491).

Of this 26%, approximately 77% will be HER2 negative (Dybdal et al. 2005) (estimated no. of new HER2 negative metastatic breast cancer patients in England; 2010: 7,956, 2011: 8,018, 2012: 8,078).

Of these ~75% will receive 1st line chemotherapy treatment (Synovate Healthcare, 2009) (estimated no. of new HER2 negative metastatic breast cancer patients receiving 1st line chemotherapy in England; 2010: 5,967, 2011: 6,013, 2012: 6,059).

Of those patients around 46% will receive taxane based therapy (Synovate Healthcare, 2009) and are therefore eligible for treatment with bevacizumab. This equates to a predicted eligible population in England of 2,745 in 2010, 2,766 in 2011 and 2,787 in 2012.

Table 60. Estimated number of patients eligible to receive treatment in England

Assumptions	Percentage	Value 2010	Value 2011	Value 2012
Local population		**52,706,471**	**53,113,335**	**53,514,508**
Breast Cancer Incidence	**0.0754%**	**39,741**	**40,047**	**40,350**
Proportion of patients with metastatic disease	**26%**	**10,333**	**10,412**	**10,491**
Proportion HER2 negative	**77%**	**7,956**	**8,018**	**8,078**
Proportion receiving 1st line chemotherapy	**75%**	**5,967**	**6,013**	**6,059**
Proportion taxane based	**46%**	**2,745**	**2,766**	**2,787**
Eligible population		**2,745**	**2,766**	**2,787**

Wales

The breast cancer incidence rate in Wales in 2006 was 0.083% (Cancer Research UK, February 2006). For the purposes of this evaluation it is assumed that this rate is representative of the incidence rate in 2010, 2011 and 2012.

The population of Wales is predicted to be 3,037,557 in 2010, 3,052,787 in 2011 and 3,067,657 in 2012 (GAD, 2006-based principal projections). A breast cancer incidence rate of 0.083% will result in 2,521 new breast cancer patients in 2010, 2,534 in 2011 and 2,546 in 2012.

The same assumptions as were applied to English patients were applied to Welsh patients in order to derive a predicted eligible population of 174 in 2010, 175 in 2011 and 176 in 2012.

Table 61. Estimated number of patients eligible to receive treatment in Wales

Assumptions	Percentage	Value 2010	Value 2011	Value 2012
Local population		**3,037,557**	**3,052,787**	**3,067,657**
Breast Cancer Incidence	**0.083%**	**2,521**	**2,534**	**2,546**
Proportion of patients with metastatic disease	**26%**	**656**	**659**	**662**
Proportion HER2 negative	**77%**	**505**	**507**	**510**
Proportion receiving 1st line chemotherapy	**75%**	**379**	**380**	**382**
Proportion taxane based	**46%**	**174**	**175**	**176**
Eligible population		**174**	**175**	**176**

England and Wales

Predicted eligible population in England and Wales:

2010: 2,745 + 174 = **2,919**
2011: 2,766 + 175 = **2,941**
2012: 2,787 + 176 = **2,963**

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

It was assumed that the proportion of first line chemotherapy patients receiving a taxane based regimen would remain constant at 46% in 2010, 2011 and 2012.

In the absence of NICE approval it was assumed that the market share of taxane based therapy currently held by each regimen would remain constant for the period of analysis. These proportions were taken from perception based market research commissioned by Roche (Synovate Healthcare, 2009).

Table 62. Assumed market shares of taxane based regimens in the absence of NICE approval of bevacizumab + paclitaxel combination therapy

Treatment Regimen	2010	2011	2012
Docetaxel	**66.6%**	**66.6%**	**66.6%**
Paclitaxel	**15.3%**	**15.3%**	**15.3%**
Paclitaxel + gemcitabine	**3.6%**	**3.6%**	**3.6%**
Paclitaxel + bevacizumab	**0%**	**0%**	**0%**
Other taxane	**14.5%**	**14.5%**	**14.5%**

The above proportions were applied to the eligible population figures calculated in section 8.3 to determine the number of patients likely to receive each treatment regimen each year in the absence of NICE approval.

Table 63. Patients receiving each taxane based regimen in the absence of NICE approval of bevacizumab + paclitaxel combination therapy

Treatment Regimen	2010	2011	2012
Docetaxel	**1,944**	**1,959**	**1,973**
Paclitaxel	**447**	**450**	**453**
Paclitaxel + gemcitabine	**105**	**106**	**107**
Paclitaxel + bevacizumab	**0**	**0**	**0**
Other taxane	**423**	**426**	**430**
Total	**2,919**	**2,941**	**2,963**

8.4 What assumption(s) were made about market share (where relevant)?

It was assumed that given NICE approval, bevacizumab uptake, and the source of that uptake, would mirror that in the UK private sector. It was assumed that the market share held by taxane treatments outside the scope of this appraisal remained constant throughout the period of evaluation.

Table 64. Assumed market shares of each regimen in those 1st line metastatic breast cancer patients suitable for treatment with a taxane given NICE approval of bevacizumab + paclitaxel combination therapy

Treatment Regimen	2010	2011	2012
Docetaxel	**66.4%**	**57%**	**42.5%**
Paclitaxel	**11%**	**2%**	**0.5%**
Paclitaxel + gemcitabine	**3.6%**	**1.5%**	**0.5%**
Paclitaxel + bevacizumab	**4.5%**	**25%**	**42%**
Other taxane	**14.5%**	**14.5%**	**14.5%**

The above proportions were applied to the eligible population figures to estimate the number of patients likely to receive each treatment regimen in each year.

Table 65. Patients receiving each taxane based regimen given NICE approval of bevacizumab + paclitaxel combination therapy

Treatment Regimen	2010	2011	2012
Docetaxel	**1,938**	**1,676**	**1,259**
Paclitaxel	**321**	**59**	**15**
Paclitaxel + gemcitabine	**105**	**44**	**15**
Paclitaxel + bevacizumab	**131**	**735**	**1,244**
Other taxane	**423**	**426**	**430**
Total	**2,919**	**2,941**	**2,963**

8.5 What unit costs were assumed? How were these calculated?

Costing incorporated the average PASA price of paclitaxel (as per discussions with NICE) and a 10g cap on bevacizumab (as is current practice in the UK private sector). Aside from paclitaxel, all other drug costs were taken from BNF 58. The administrative costs of treatment were taken from National Reference Costs 2007/2008. The mean total costs of each regimen were taken from the economic model and combined with the population figures calculated above in order to produce the total budget impact of NICE approval.

The table below is provided to demonstrate the acquisition, administration and total cost of each regimen produced by the model. As the economic model incorporated cost beyond drug and administration costs alone (including the cost of supportive care, adverse events, end of life costs etc) the total cost of each regimen is greater than the sum of the administration and drug costs alone.

Table 66. Average total drug and administration costs for each regimen

	Bevacizumab + paclitaxel	Docetaxel	Paclitaxel	Gemcitabine + paclitaxel
Cost of bevacizumab (£)	17,352	**0**	**0**	**0**
Administration cost of bevacizumab (£)	110	**0**	**0**	**0**
Cost of paclitaxel (£)	649	**0**	**475**	**352**
Administration cost of paclitaxel (£)	5,782	**0**	**4,232**	**2,073**
Cost of docetaxel (£)	0	**6,723**	**0**	**0**
Administration cost of docetaxel (£)	0	**1,867**	**0**	**0**
Cost of gemcitabine (£)	0	**0**	**0**	**4,987**
Administration cost of gemcitabine (£)	0	**0**	**0**	**1,748**
Total cost of regimen (£)	40,816	**25,057**	**20,830**	**25,282**

Table 67. 2011 Budget impact of approval in England and Wales (including all direct costs associated with each regimen)

	NICE approval	Otherwise
Total cost of docetaxel monotherapy	£48.57m	£48.71m
Total cost of paclitaxel monotherapy	£6.69m	**£9.30m**
Total cost of paclitaxel + gemcitabine combination therapy	£2.66m	**£2.66m**
Total cost of paclitaxel + bevacizumab combination therapy	£5.36m	**£0**
Total cost of taxane therapy within scope of appraisal	£63.27m	**£60.67m**

2010 Budget impact: £63.27m - £60.67m = £2.60m

Table 68. 2011 Budget impact of approval in England and Wales (including all direct costs associated with each regimen)

	NICE approval	Otherwise
Total cost of docetaxel monotherapy	£42.00m	£49.08m
Total cost of paclitaxel monotherapy	£1.23m	**£9.37m**
Total cost of paclitaxel + gemcitabine combination therapy	£1.12m	**£2.68m**
Total cost of paclitaxel + bevacizumab combination therapy	£30.02m	**£0**
Total cost of taxane therapy within scope of appraisal	£74.36m	**£61.13m**

2011 Budget impact: £74.36m - £61.13m = £12.23m

Table 69. 2012 Budget impact of approval in England and Wales (including all direct costs associated with each regimen)

	NICE approval	Otherwise
Total cost of docetaxel monotherapy	£13.55m	£49.44m
Total cost of paclitaxel monotherapy	£0.31m	**£9.44m**
Total cost of paclitaxel + gemcitabine combination therapy	£0.37m	**£2.70m**
Total cost of paclitaxel + bevacizumab combination therapy	£50.79m	**£0**
Total cost of taxane therapy within scope of appraisal	£83.02m	**£61.58m**

2012 Budget impact: £83.02m - £61.58m = **£21.44m**

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

Paclitaxel plus bevacizumab is a combination therapy. Paclitaxel is administered once a week for three weeks of a 28-day cycle, for which hospital visits are necessary. Bevacizumab is administered every two weeks and so would not require any additional hospital visits, although at the visits where both paclitaxel and bevacizumab are administered, additional time (on average 30 minutes) will be required for infusions. Before treatment an additional 20 minutes of pharmacist time will be required for preparation of bevacizumab. These requirements are unlikely to incur significant additional resource costs.

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

It is predicted that upon approval by NICE bevacizumab + paclitaxel combination therapy will displace a proportion of gemcitabine + paclitaxel combination therapy. Whilst the addition of bevacizumab will require additional NHS resources this displacement will result in a lower budgetary impact of gemcitabine.

Given NICE approval it is estimated that in 2011, 62 patients will no longer require gemcitabine and in 2012, 92 patients will no longer require gemcitabine. As bevacizumab is more expensive than gemcitabine this displacement will not represent a net saving to the NHS.

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

The extended PFS period provided by bevacizumab will delay future progression associated costs for the period of that extension. As bevacizumab is additive to the current standard of care it is unlikely to result in any resource savings.

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