THE USE OF PACLITAXEL IN THE MANAGEMENT OF EARLY STAGE BREAST CANCER

THE EVIDENCE REVIEW GROUP'S REPORT

The Evidence Review Group consists of:

Centre for Health Economics, University of York

S Griffin, G Dunn, S Palmer

&

Regional Drug and Therapeutics Centre (Newcastle)

K Macfarlane, S Brent, A Dyker, S Erhorn, C Humphries, S White, W Horsley, L Ferrie, S Thomas

About the authors:

The ERG is a collaboration between two centres, the Regional Drug and Therapeutics Centre (RDTC) and the Centre for Health Economics (CHE).

The RDTC was established in 1991 to promote safe effective prescribing and economical drug usage, and to provide a source of independent authoritative advice on pharmaceutical and therapeutic issues throughout the former Northern and Yorkshire region. The RDTC co-ordinates prescribing activities, provides a poisons and medicine information service and is the teratology information service for the UK. The Centre is one of four NHS regional monitoring centres for the Medicines and Healthcare Regulatory Authority (MHRA).

CHE is a research unit of the University of York. The Centre's aim is to undertake high quality research that is capable of influencing health policy decisions. The largest programme of work at CHE is that on economic evaluation and health technology assessment which focuses on a range of methodological and applied work. This includes full technology assessment reviews and evidence review reports for the National Institute for Health and Clinical Excellence (NICE). Recent assessment reports for NICE include treatments for prostate cancer, psoriasis and psoriatic arthritis.

Contact the authors:

Regional Drug and Therapeutics Centre,
Wolfson Unit, Claremont Place, Newcastle upon Tyne, NE2 4HH
Centre for Health Economics
Alcuin 'A' Block, University of York, Heslington, York, YO10 5DD

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Conflicts of interest:

The authors to this report have no conflicts of interest. Mark Sculpher - a member of the ERG who did not participate in this review – has financial links with a consultancy which has undertaken work for BMS although not relating to paclitaxel.

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1. Introduction

This document critically evaluates the evidence submission, from Bristol-Myers Squibb Pharmaceuticals Ltd (BMS), on the clinical and cost-effectiveness of paclitaxel (Taxol®) for adjuvant treatment of early breast cancer.[1] This report identifies the submission's strengths and weaknesses, supplemented, where appropriate, with our own analysis. Clinical experts were asked to advise the Evidence Review Group (ERG) to help inform the review.

1.1 Scope of the submission

The perceived aim of the BMS submission was to evaluate the clinical and cost-effectiveness of paclitaxel for the licensed indication of the treatment of early stage, operable, node positive breast cancer following 4 cycles of anthracycline and cyclophosphamide therapy.[2]

1.2 Summary of submitted clinical evidence

Of the 3 clinical trials included in the submission report, 2 were fully published.[3 4] These trials aimed to determine whether 4 cycles of paclitaxel following 4 cycles of doxorubicin and cyclophosphamide (AC-P) would prolong disease-free survival (DFS) and overall survival (OS). Improvements of 5% (HR 0.83, 95% CI 0.73 to 0.94) and 4.2% (HR 0.83, 95% CI 0.72 to 0.95) in DFS and 4% (HR 0.82, 95% CI 0.71 to 0.95) and 0.8% (HR 0.93, 95% CI 0.78 to 1.12) in OS were seen in the 2 published trials. Both showed that the addition of 4 cycles of paclitaxel to 4 cycles of AC chemotherapy resulted in modest improvements in these 2 endpoints. The unpublished study[5] evaluated 4 cycles of AC followed by paclitaxel or docetaxel in breast cancer. This trial had insufficient data presented to fully assess the validity of the study, but did show that there were no statistically significant differences in DFS or OS between any group.

1.3 Summary of submitted cost-effectiveness evidence

The submission included a *de novo* economic evaluation of paclitaxel for adjuvant therapy in early breast cancer, which the manufacturer's state was based on 2[3 5] of the 3 trials submitted as clinical evidence. Of the explicitly included trials, 1 was fully published and the other was unpublished. A probabilistic Markov state-transition model was used to compare the cost-effectiveness of the treatment strategies included in the 2 clinical trials. The measure of health benefit was quality-adjusted life-years (QALYs) and the model included

direct costs using a UK NHS perspective. The primary analysis compared AC-P to 4 cycles AC. The reported incremental cost-effectiveness ratio (ICER) for this comparison was £4,726 per additional QALY for AC-P compared to 4 cycles AC.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

The sections containing descriptions of individual studies did accurately reflect the data presented within the clinical trials that were considered in the manufacturer's submission. The overall economic model structure was appropriate for the decision problem, and the data sources used to inform the model were appropriate from a UK NHS perspective.

1.4.2 Weaknesses

The ERG felt that the BMS submission was generally of poor quality with key omissions. The major flaw in the submission was the absence of a systematic literature review, as instructed by NICE in the draft guidance.[6] BMS limited the clinical effectiveness in the submission to 3 studies, and it was unclear, without the ERG undertaking a full systematic review, whether they had considered all the relevant literature. This same selective use of available evidence was apparent in the economic evaluation. There was a tendency throughout the trials section to refer to relative risk rather than absolute risk and relevant *p* values were not quoted. This had the effect of exaggerating any possible benefits of treatment. Whilst the trial evidence around paclitaxel appears to show modest benefit, the trials themselves may not be directly applicable to the clinical situation that these patients are likely to face.

A further shortcoming of the submission was in not clearly defining the choice of comparator(s). This is important in determining relative efficacy and, if not clearly stated, affects the underlying discussions throughout the document. The comparators that were included in the cost-effectiveness analysis were not considered by the ERG to represent current treatment in the UK NHS or relevant licensed alternatives, and 4 cycles AC may be regarded as a weak comparator in this patient population.

The submission did not consider identifiable sub-groups of patients defined by prognostic factors that strongly influence the baseline risk of future events. Instead, the results are presented for the average patient recruited to the clinical trials included in the analysis, and this may conceal wide variation in the cost-effectiveness of paclitaxel according to baseline risk.

There were a number of typographical errors, minor discrepancies in data, modelling errors and a number of statements throughout the document which were not supported by valid references. Overall, the submission report was not of the quality and detail that the ERG had expected; consequently, parts of the submission needed to be repeated by the ERG and a lot more time was spent on areas that should have been appropriately completed by BMS.

1.4.3 Areas of uncertainty

Within the context of this review, it is impossible for the ERG to make appropriate comparisons between paclitaxel and relevant anthracycline-containing chemotherapy regimens or the licensed dose of docetaxel. It is, therefore, impossible for the ERG to predict what effect including these comparators would have on the cost-effectiveness of paclitaxel for adjuvant treatment of early breast cancer.

1.5 Key issues

- The submission did not include a systematic review for clinical or cost-effectiveness evidence:
  - as a result, potentially relevant trials and previously published studies were omitted.
- The submission did not include relevant comparators:
  - the main comparator did not represent standard care in the UK NHS;
  - a large number of relevant comparators were omitted, including docetaxel, another taxane, as licensed for the same indication.
- The manufacturer did not consider potentially important patient sub-groups defined by baseline risk:
  - the cost-effectiveness result in the average overall patient population may conceal important variation between sub-groups

Chapter 2
Background

2.1 Description of the underlying health problem

In England & Wales breast cancer is the most common malignancy and cause of cancer mortality in females [7-9] with 39,175 new cases of breast cancer registered in 2003, [8-10] representing a crude incidence rate of 74 per 100,000 population. In the same year, over 11,000 women died of breast cancer.[7-10] This is a cancer that affects predominantly middle-aged to older women. The incidence of new cases in 2003 in women younger than 30 years was less than 0.4% and the incidence in males represented less than 1% of all new cases. [8-10] More than 80% of new cases are diagnosed in women aged 50 and over, [7 8 10] with the peak age range for diagnosis in females being 55 to 59 years (5,395 out of 38,864 new cases in 2003). [8 10] The NHS Breast Screening Programme is offered to all women over the age of 50 years, which partially explains the increased incidence of new cases in females over this age; for example, 4,553 women aged 50 to 54 years were diagnosed with breast cancer in England & Wales in 2003. [8 10]

The five-year age-standardised relative survival rate up to the end of 2001 for adult female patients (15-99 years) diagnosed with breast cancer between 1996-99 in England & Wales was 77.5%, with a trend towards increasing rates of survival over the years. [11]

An invasive breast cancer is one in which there is dissemination of cancer cells outside the basement membrane of the ducts and lobules into the surrounding adjacent normal tissue.[12]

The presence or absence of involved axillary lymph nodes is the single best predictor of survival of breast cancer, and important treatment decisions are based on it. Both the number of involved nodes and the level of nodal involvement predict survival from breast cancer.[13] When invasive breast cancer is diagnosed the extent of the disease should be assessed and the tumour staged. The two staging classifications in current use are the tumour node metastases (TNM) system and the International Union Against Cancer (UICC) system which incorporates the TNM classification (Appendix 1). Prognosis in breast cancer relates to the stage of the disease at presentation.[12]

Data published in 2003 indicated a prevalence of early stage (Appendix 2) node-positive breast cancer (T1-3, N+, M0) in two regional UK populations (n=559) of approximately 21% of all presenting breast cancers; the same study reported a pan-European (n=4,478) incidence rate of 31%.[14] An earlier (1997) UK study (n=1,440) reported that 49.8% of all presenting breast cancers were node-positive at the time of diagnosis.[15]

Where surgery is considered appropriate treatment for breast cancer, a number of options are available with differing levels of breast tissue conservation. When chemotherapy is administered after surgery of any type, it is known as adjuvant chemotherapy. When chemotherapy is administered before surgery, it is known as neo-adjuvant chemotherapy.[16]

Ensuring that adjuvant therapy is always offered to women with primary breast cancer when appropriate could reduce recurrence and improve survival rates.[17] In 2002, the National Institute of Clinical Excellence recommended that almost all patients with invasive breast cancer should be offered adjuvant systemic therapy (hormone therapy and/or chemotherapy).[17] Women at intermediate or high risk of recurrence, dictated by primary tumour size, extent of nodal involvement and tumour grade, who have not had neo-adjuvant chemotherapy, should normally be offered four to eight cycles of multiple-agent chemotherapy which includes an anthracycline.[17] Adjuvant! Online (www.adjuvantonline.com)[18 19] is a well respected cancer website designed to be used by healthcare professionals. Its main purpose is to help physicians make estimates of probable benefit derived by giving adjuvant therapy to individual cancer patients.[20] Its purpose is intended to be both practical and educational.[20] Adjuvant! online classifies key prognostic predictors as tumour size, number of involved nodes, histologic grade and oestrogen receptor status.[20]

2.2 Critique of the manufacturer's description of the background

The BMS submission did not provide a detailed background section. The purpose of the background was to summarise and contextualise the decision problem, which was not clearly done (section 1.1).[1] This is discussed further in the next section. The description of the technology under assessment (section 1.2) was detailed and appropriate, and did cover all the relevant aspects. Current treatment options were not discussed in detail, and relevant comparators were not clearly indicated, as discussed further in this report. This lack of clear comparators meant that the question around the main differences in indications, contraindications etc. was not answered, and differences were not shown.

Chapter 3
Defining the Decision Problem

3.1 Intervention

The scope for this single technology assessment (STA) was not clearly defined in the BMS submission, and BMS did not summarise the decision problem. They referred to the main licensed indications and summarised the clinical trial results, but did not explicitly describe the main decision problem facing the NHS. The ERG made the decision to look at the scope based on the licensed indication, i.e. the use of paclitaxel for the treatment of node positive, breast cancer following anthracycline and cyclophosphamide therapy. The licensed dose is 175 mg/m^2 every 3 weeks for four courses.[2] Additionally, paclitaxel is licensed for treating ovarian cancer, advanced non-small cell lung cancer and AIDS related Kaposi's Sarcoma.[2] Paclitaxel is manufactured in the UK as Taxol® (BMS) and is now also available generically (from Mayne Pharma plc). The list prices at time of writing are comparable, with prices of the generic being £112.20, £336.60 and £1009.80 and Taxol® as £116.05, £347.82 and £1043.46 for the 5ml, 16.7ml and 50ml vials respectively.[21]

3.2 Patient population

The manufacturer defined the patient population as women who have been diagnosed with early stage operable breast cancer who are candidates for cytotoxic chemotherapy regimens regardless of oestrogen receptor status. The ERG felt this definition to be too broad and not clearly defined. It is important to consider which sub-group(s) of patients may be most likely to benefit from paclitaxel treatment. It would appear that this may be done by linking into the individual risk profile of the patient, concentrating on moderate to high-risk patients. Risk factors would include factors such as age, nodal involvement and tumour size.

3.3 Comparators

In their submission, BMS stated that the choice of adjuvant therapy in the UK varied by centre and clinician, but for this submission, the main regimens for comparison were doxorubicin and cyclophosphamide followed by paclitaxel (AC-P), versus doxorubicin and cyclophosphamide (AC).

Paclitaxel and docetaxel are the only two members of the 'taxane' family, and docetaxel is licensed for the same indication (in combination with doxorubicin and cyclophosphamide) for the adjuvant treatment of patients with operable node- positive breast cancer.[22] Docetaxel is therefore an appropriate comparator.

The Taxol® Summary of Product Characteristics (SPC) regards extended AC therapy to be an alternative to adjuvant treatment with paclitaxel, so further cycles of AC treatment could also be considered as an active comparator.[2] The BMS submission did not clearly state that they considered docetaxel and extended AC treatment to be the key comparators.

Common anthracycline-based regimens used for adjuvant therapy in the UK include FEC (5 fluorouracil, epirubicin, and cyclophosphamide) and doxorubicin with cyclophosphamide (AC).[17] Adjuvant chemotherapy that includes an anthracycline, such as doxorubicin or epirubicin, has been reported to be more effective than the cyclophosphamide, methotrexate and 5-fluorouracil regimen (CMF).[23] Compared with CMF, anthracycline-containing regimens reduced the recurrence rate by 11% (p=0.001)[24] and increased five-year survival rates from 69% to 72% (p=0.02).[23] A recent analysis also demonstrated that the absolute survival benefit is 3% at five years, and 4% at ten years.[24] The number of patients receiving treatment has risen sharply over the last few years and many institutions have already moved away from the use of CMF for adjuvant therapy.[17] One particular anthracycline regimen is 5-fluorouracil, doxorubicin and cyclophosphamide (FAC). This is better tolerated than CMF and fewer cycles are necessary to produce an equivalent level of benefit.[17]

Discussions with the clinical advisors to the ERG suggest that 4 cycles AC may not now be the optimal chemotherapy regimen in this higher risk group of patients; other chemotherapy regimens may now be more appropriate treatment of the early stages of the disease.[25] These include:

- FEC regimen
- FAC regimen
- ECMF (epirubicin, cyclophosphamide, methotrexate and 5-Fluorouracil)
- ACMF (doxorubicin, cyclophosphamide, methotrexate and 5-Fluorouracil)

Adjuvant! Online considers 4 AC to be '1st generation' with modest activity compared to no therapy or roughly equal to CMF. It considers 4 AC + 4 T (paclitaxel), along with 6 x FEC_{100} and 6 x FAC, to be '2nd generation' and superior in efficacy to 1st generation regimens.

In higher risk patients, the choice of 4 cycles of AC as a chemotherapy regimen does raise questions as to the relevance of much of the research data presented within the submission, as the additional benefit demonstrated with paclitaxel may not have been seen or its

magnitude significantly reduced had paclitaxel been compared with a more aggressive and more efficacious chemotherapy regimen.

If the AC regimen is now considered to be inferior to current more modern modalities of treatment it could be argued that there is a need for further research to assess the benefit of taxanes in conjunction with these new regimens, before making any recommendation for use outwith clinical trials.

The license does, however, stipulate that paclitaxel be used in combination with the AC regimens so it is not surprising that the data demonstrating putative benefit evaluates patients who have received AC along with paclitaxel.[2] This is a rapidly moving area of medicine where complex combinations of treatment are constantly being investigated.

3.4 Trial Outcomes

Key outcomes that were considered in the clinical trials were disease free survival (DFS) and overall survival (OS). OS is considered to be the 'gold standard' but DFS is also felt to be a suitable measure of outcome.[25] Specific adverse events that are analysed in the trials include neurological toxicity, granulocytopenia, febrile neutropenia and thromboembolic events. Cardiac dysfunction and acute myelogenous leukaemia or myelodysplastic syndrome (AML/MDS) are additionally considered. Health-related quality of life (HRQoL) was not a key consideration in these trials. The principal outcome for the economic analysis was cost per quality-adjusted life-year (QALY). The manufacturer did not comment on whether the trial data could inform the health economic outcomes. However, as no measures of utility were included in the clinical trials, a model is an appropriate mechanism for estimating QALYs from the primary clinical outcomes.

3.5 Any other relevant factors

The scope for this STA was not clearly defined in the BMS submission. Beyond a brief description of the intervention and the patient population, the manufacturer did little to define the decision problem, and no other relevant factors were considered. By failing to provide adequate detail about all aspects of the decision problem the manufacturer increased the difficulty in the task of critiquing their approach.

Chapter 4
Clinical Effectiveness

The ERG felt that in order to fully effectively comment on the BMS submission, and in view of the lack of systematic review, a full detailed search needed to be undertaken. This would highlight any trials that had been omitted, and give an accurate picture of the evidence base. Systematic reviews were also included in the search, to gain a feel for what overall opinions were on this issue. The objectives were to;

- Undertake a detailed systematic review of studies.
- Critically analyse the relevant trials, regardless of whether BMS had included them or not.
- Summarise the main points from any systematic reviews found.

Additionally, the BMS submission included three sets of international guidelines, and it was also felt important to review their main points, as they were part of the whole submission. The following section outlines the search strategy, the critical analysis of all relevant trials and the main points from both the systematic reviews and international guidelines.

4.1 Search Strategy

The submission did not contain a systematic review of studies, although a full search strategy was undertaken by the ERG and is attached in Appendix 3. Few additional studies were found which added to the evidence base regarding efficacy, however their inclusion would have added to the safety data. The failure to perform a systematic search was a key omission in the BMS submission. It was unclear on what basis they had chosen the three trials they included, and what trials (if any) they omitted and why. No further explanation was given as to why a systematic review was not undertaken.

The submission clearly stated that the manufacturer's did not perform a systematic literature review; however they stated inclusion and exclusion criteria as being “Comparative studies with paclitaxel for the adjuvant treatment of operable node positive breast cancer in women with outcomes data on DFS and OS”. The inclusion and exclusion criteria that the ERG used are included in Appendix 3.

Table 4.1 below lists the trials included and excluded in the BMS submission together with some key points for each trial;

Table 4.1 Summary of potentially relevant trials included and excluded from manufacturer's submission

Included Trials	Key Points
Henderson I C *et al*[3]	• Fully published trial • Showed the addition of paclitaxel after completion of AC significantly improved DFS and OS in patients with early breast cancer.
Mamounas E P *et al*[4]	• Fully published trial • Showed the addition of paclitaxel after completion of AC significantly improved DFS but not OS in patients with early breast cancer.
Sparano J A *et al*[5]	• Available as an abstract only, data has not yet been fully published • No significant differences seen in outcome, DFS or mortality

Excluded Trials	Key Issues
Buzdar A U *et al*[26]	• Results were classed as interim • This trial is the only one that has an active comparator - the substitution of paclitaxel for 4 cycles of FAC • DFS at 4 years was not significant
Citron M L *et al*[27]	• Did not compare paclitaxel to alternative treatments or placebo

Tables 4.2, 4.3 and 4.4 summarise the main aspects of the three included trials;

Table 4.2 Summary of trial CALBG 9344

Abbreviations key: AC: Doxorubicin and Cyclophosphamide, **A/E**: Adverse Effect, **AML/MDS**: acute myelogenous leukaemia or myelodysplastic syndrome, **ARR**: Absolute Risk Reduction, **BC**: Breast Cancer, **CI**: Confidence Intervals, **CYC**: Cyclophosphamide, **DFS**: Disease Free Survival, **DMC**: Data Monitoring Committee, **DOX**: Doxorubicin, **DTX**: Docetaxel, **ECOG**: Eastern Cooperative Oncology Group, **ER**: Estrogen receptor, **HR**: Hazard Ratio, **MC**: Multi-centre, **OS**: Overall Survival, **PR**: Progesterone receptor, **PTX**: Paclitaxel **RCT**: Randomised, Controlled Trial, **RR**: Relative Risk.

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Outcomes	Results	Adverse Effects
Henderson I C *et al.* CALGB 9344	This study was an RCT. To answer 2 questions in one study it was a 3 x 2 factorial design.	3121 women were randomised to one of 3 doses of DOX (60, 75 or 90 mg/m^2) + CYC (600 mg/m^2) for 4 cycles (AC). A 2nd randomisation allocated women to a further 4 cycles of PTX (175 mg/m^2) or no further therapy.	Eligible patients had operable BC with clear surgical margins and metastases to axillary nodes. Systemic therapy started within 84 days of the patient's last surgery.	Not Stated	The primary end point was duration of DFS. OS and toxicity assessment were secondary end points.	At 5 years DFS and OS were superior for patients receiving PTX in addition to AC (DFS - 70% vs 65%, p=0.0023, and OS - 80% vs 77%, p=0.0064). There was no interaction between DOX dose and the addition of PTX.	98% patients who began AC completed all 4 cycles, dose reductions & delays in initiating treatment were significantly increased at higher DOX doses (p<0.0001) Severe neutropenia, thrombocytopenia, anaemia, blood or platelet transfusions and hospitalisations increased in frequency with each DOX dose increase (p<0.0001). 58 patients assigned to receive PTX did not receive any; the most common reason was withdrawal of consent (41 out of 58 patients). 92% of the patients who started PTX completed all 4 cycles

Table 4.3 Summary of trial NSABP B-28

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Outcomes	Results	Adverse Effects
Mamounas E P *et al.* NSABP B-28	This study was an RCT and was designed to determine whether four cycles of adjuvant PTX after 4 cycles of adjuvant AC would prolong DFS and OS compared with four cycles of AC alone	A total of 3,060 women were randomly assigned to AC (1,529) and AC→PTX (1,531)	Eligible patients had resected, operable adenocarcinoma confined to the breast & ipsilateral axilla on clinical examination, & were randomly assigned within 63 days from diagnosis. They had to have undergone either lumpectomy + axillary node dissection or modified radical mastectomy, and tumour had to be invasive adenocarcinoma with at least 1 positive axillary lymph node. ER and PR status was performed before assignment. Patients needed to have normal haemotologic, hepatic & renal parameters & a life expectancy of at least 10 yrs (excluding cancer diagnosis)	Patients with a previous history of invasive BC or ductal carcinoma in-situ (in either breast) were ineligible, as were patients who had received any prior radiation, chemotherapy, immunotherapy or hormonal therapy for their present BC.	The primary end points were DFS and OS.	There were 463 DFS events in the AC arm and 400 in the AC→PTX arm. The addition of PTX reduced the risk of a DFS event by an ARR of 4.2% (RR 0.83; 95% CI, 0.72-0.95; p=0.006). The 5-year DFS for AC patients was 72% +/- 2% compared with 76% +/- 2% for those in the AC→PTX arm. OS – There were 255 deaths in the AC arm and 243 in the AC→PTX arm. The addition of PTX gave an ARR of 0.8% (RR 0.93; 95% CI, 0.78-1.12; p=0.46). The 5 year OS was 85% +/- 2% for both arms.	7 patients died, where treatment couldn't be excluded as a contributing factor. 5 occurred in AC patients only, 2 in AC→PTX. The most common grade 3 or greater toxicity during PTX therapy included neurosensory toxicity in 15% patients, neuromotor toxicity in 7%, arthralgia and/or myalgia in 12%, day 1 granulocytopenia in 3%, febrile neutropenia in 3% & thromboembolic events in 1%. Severe hypersensitivity reactions occurred in 1% of patients during PTX administration. Incidence of grade 3 or higher cardiac dysfunction was 1% in AC & 0.9% in AC→PTX. There were 8 cases of AML/MDS. 6 occurred in AC→PTX and 2 in AC.

Table 4.4 Summary of trial NABCI E1199

Reference	Design	Intervention	Inclusion criteria	Exclusion Criteria	Outcomes	Results	Adverse Effects
Sparano J A *et al*. NABCI E1199	This was a large phase III, MC, RCT. It was designed to compare the effectiveness of adjuvant PTX with DTX, and the effectiveness of every 3 week with weekly adjuvant taxanes therapy in patients with operable BC. After a median follow-up of 46.5 months the ECOG DMC advised release of the data at the fourth planned interim analysis. However, no references to the criteria used for early reporting are given.	All patients received DOX (60mg/m^2 IV.) and CYC (600mg/m^2 IV.) every 3 weeks for 4 courses (weeks 1-12). Arm (I): Beginning at week 13, patients receive PTX (175mg/m^2 IV.) over 3 hours every 3 weeks for 4 courses. Arm (II): Beginning at week 13, patients receive PTX (80mg/m^2 IV.) over 1 hour weekly for 12 weeks. Arm (III): Beginning at week 13, patients receive DTX (35mg/m^2 IV.) over 1 hour weekly for 12 weeks. Arm (IV): Beginning at week 13, patients receive DTX (100mg/m^2 IV.) over 1 hour every 3 weeks for 4 courses.	Eligible patients included women with histologically confirmed operable axillary node-positive or high-risk (tumour at least 2 cm) node-negative BC.	Not Stated	The primary endpoint was DFS, defined as local, regional, and/or distant relapse, secondary primary BC, or death without recurrence.	There was no significant differences in the DFS when comparing taxane treatment arms (HR, 0.985; p=0.83) or dosing schedule, once weekly versus every 3 weeks (HR, 1.043; p=0.54). When comparing the 'standard' reference arm (arm II) to the other arms the HR was 1.20 (95% CI 0.99-1.46; p=0.06) for arm I, HR 1.13 (0.94-1.36; p=0.20) for arm IV, and HR 1.03 (0.85-1.23; p=0.78) for arm III, respectively.	There was a higher incidence of grade 3 or 4 A/E's in those patients receiving the larger dose of PTX compared to receiving the smaller dose (24% & 6% vs. 24% &.4%, for arm II and I, respectively). The incidence of grade 3 A/E's was lower, and the incidence of grade 4 higher in those receiving the larger dose of DTX compared to the smaller dose (21% & 50% vs. 39% & 6%, for arm IV and III, respectively. Overall neutropenia was more common with DTX exposure compared to PTX. Other grade 3 or 4 A/E's occurring in at least 5% of patients were: infection, stomatitis, fatigue and tearing.

4.2 BMS submission trial analysis

4.2.1 CALGB (Henderson C I et al) study [3]

Trial summary

This trial analysed whether there was any advantage to increasing the dose of doxorubicin in a commonly used chemotherapy regimen (AC) for patients with recently diagnosed breast cancer and histologically involved lymph nodes, and whether there was any advantage in adding paclitaxel sequentially to this regimen administered at any doxorubicin dose level. A structured critical appraisal of this trial is attached in Appendix 4.

The published trial data showed that the addition of four cycles of paclitaxel after the completion of a standard course of AC was associated with a modest improvement in DFS and OS of patients with early breast cancer, but no benefit was seen with increasing doses of doxorubicin.

Important trial points

Key aspects of this trial include;

- The dose of paclitaxel used was the current licensed dose (175mg/m^2).

- Patients in this trial had a high use of tamoxifen following chemotherapy – 94% of patients who were ER or PR positive and 21% of patients who were receptor negative. This equated to 69% of patients overall.

- There was inequality in terms of the length of treatment – there was no active comparator to paclitaxel; it was a comparison of paclitaxel vs. no further treatment.

- Treatment groups were well balanced in terms of prognostic indicators. Risk reductions were however repeatedly quoted in terms of relative risks. The absolute difference in 1 year DFS and OS between the AC and AC plus paclitaxel arms was 3% and 1% respectively. The trial quoted an improvement of 5% in DFS and 3% in OS was evident at five years. However, calculations by the ERG showed improvements of 5% in DFS and 4% in OS at five years.

- At five years DFS and OS were superior for patients receiving paclitaxel in addition to AC (70% vs 65%, p=0.0023, and 80% vs 77%, p=0.0064). The hazard ratio of OS

(the secondary endpoint) is quoted to be 0.82 with a relative risk reduction of 18% and a P value of 0.006.

Critique of the BMS submission

The majority of the submission was accurate according to the data in the published trial, and was a fair interpretation of the trial. Specific points include;

- There was no mention of absolute risk reductions (ARRs) in the submission, only the relative reductions/improvements.

- There were some differences in the way some figures were reported, e.g. on page 19,[1] the submission refers to '3,170 women were randomized', however the published trial refers to '3,121 women were randomly assigned'. The discrepancy occurs because 49 patients did not receive any protocol therapy.

- The submission refers to the primary endpoints as being DFS and OS, however, in the published trial, OS was actually a secondary endpoint.

- Much of the safety data, quoted in the submission, was not published. There were some inconsistencies in the figures quoted e.g. the trial states that '98% of patients who began AC treatment completed all four cycles of therapy" however the submission stated on page 42 that '97% and 96% of patients received 4 courses of AC in the AC and AC-P arms respectively.

- Regarding the interpretation of the clinical evidence (on page 49), this is fairly accurate, but it generalises as 'significant clinical benefit' rather than being specific on what the magnitude of that benefit. It would have been useful if this section had been more specific, quoting ARRs and primary outcomes in the key trials.

Discussions with clinical experts working in oncology suggest that DFS is an appropriate marker of efficacy as all patients who develop distant disease are likely to die of breast cancer. These modest effects are probably just clinically significant, but comments from both the expert oncologists suggested that benefits less than 5% for DFS and prolonged follow-up are probably not considered clinically significant, however, individual patient characteristics would need to be taken into consideration as well.[25 28]

In summary, the CALGB trial was well conducted and relevant to be included in the submission, despite some submission inaccuracies. The trial showed modest improvements in DFS and OS when paclitaxel was added to the AC chemotherapy regimen.

4.2.2 NSABP B-28 (Mamounas E P et al) study[4]

Trial summary

This study aimed to determine whether four cycles of adjuvant paclitaxel after four cycles of adjuvant AC would prolong DFS and OS compared with four cycles of AC alone, in patients with resected operable breast cancer and positive axillary nodes. The primary endpoints were DFS and OS. A structured critical appraisal of this trial is attached in Appendix 5.

The published trial was a well structured RCT over a relatively long time period (5.4 years), in 3,060 patients. Primary endpoints were DFS and OS, and the endpoint of DFS was statistically significant but the endpoint of OS was not.

The trial incorporated patients with a lower risk of relapse than in the other key trial and used a higher, unlicensed dose of paclitaxel, and yet the results are of the same magnitude. There are outstanding confounding issues about the high and concurrent use of tamoxifen, and again this study does not indicate whether or not the benefit in the taxane arm was purely due to the increased duration of treatment, as there was no active comparator. This trial does not add to scientific evidence regarding use of taxanes in lymph node negative patients, as only lymph node positive patients were involved. This trial did demonstrate that the addition of paclitaxel to AC chemotherapy resulted in a significant improvement in DFS at 5 years.

Important trial points

Key aspects of the trial are summarised in the following points;

- A higher dose of paclitaxel was utilised than that currently licensed in the UK. (225mg/m^2 compared to 175mg/m^2)

- Stratification appears to have led to a good balance of prognostic factors between the comparator groups.

- Paclitaxel was compared with no additional treatment, as both groups received the same initial chemotherapy (AC), thus any possible benefit could simply be due to more prolonged treatment rather than a taxane specific effect.

- Age of patients was also relatively young with about half of patients younger than 50 years. This may be younger than most eligible patients and toxicity and beneficial effect may not be consistent with older individuals.

- There was a very high use of tamoxifen in this trial – 85% of all trial participants and tamoxifen was also administered at the start of the chemotherapy regimen. This could be a confounding issue – some evidence suggests it is better post chemotherapy, and this early use may have adversely affected the results.[29]

- Only lymph node positive patients were involved, however, the license is only for node positive patients.

- The populations in this study may have had a better overall prognosis than the CALGB trial participants, because in this trial 70% of patients had 1-3 positive nodes involved, compared to only 46% in the CALGB trial.[3]

Based on the figures reported in this published paclitaxel trial, overall DFS showed a statistically significant improvement with an ARR of 4.2% (RR 0.83; p=0.006, CI 95% 0.72-0.95). OS did not show a statistically significant improvement, with an ARR of 0.82% (RR 0.93, p=0.46, CI 95% 0.78-1.12). An appropriate subset analysis was conducted evaluating the effect of HER receptor status. There was no difference in paclitaxel effect according to receptor status.

Critique of the BMS submission

Regarding the accuracy of the submission data; the majority of the submission was accurate according to the data in the published trial, and was a fair interpretation of the trial. The submission report states there was a reduction in the death rate and does point out that it was not statistically significant. There were some additional points about the trial in the description of patients and methods, and some minor inaccuracies in other sections. The submission report omits absolute numbers and confidence intervals, although these data are quoted in the published paper.

In section 4.2.3 - Results (page 28),[1] the following statements in the submission were incomplete or misleading;

- The submission quotes “Hazards of disease recurrence over time following the first 2 years after surgery, where the highest hazards were observed, show a reduction of the risk in the AC-P arm that is maintained and is consistently lower than in the AC arm in the following years”.[1] The trial illustrates this graphically, and this statement gives no actual data, or measures of uncertainty.

- The submission refers to the hazard ratios associated with various types of first events ranging from 0.53 to 0.90, but makes no mention of corresponding confidence intervals (some of which include 1) or *p* values.

- The submission refers to the effect of paclitaxel on tamoxifen treated patients, and this data is not in the published trial. The submission states that paclitaxel prolonged DFS more in tamoxifen treated patients than in patients not treated with tamoxifen, but do not provide the actual data to support this claim.

- The submission stated that “irrespective of the endpoint (DFS or OS) and of the subset (HR status or tamoxifen treatment), the paclitaxel treated group constantly benefited more than the control group”. It is not possible to verify or quantify this statement as not all of the relevant figures are published in either the trial or the submission.

- The submission contains additional safety data not published in the trial. Where we were able to check, there are some inconsistencies with some of the figures (e.g. the submission stated that 7% of the patients who completed AC therapy did not start paclitaxel, whereas the trial stated 8.8%). It is unclear how this may affect the results.

- The information on page 47,[1] relating to the number of deaths within 30 days after the end of therapy, is new information in the submission. The information on second malignancies is also new in the submission and not published in the trial.

- Regarding the interpretation of the clinical evidence (on page 49), this appears to be accurate, but statements such as ‘significant clinical benefit’ are made without reference to what that benefit is (improvement in DFS and varying benefits in OS).

The ERG questioned the omission of this trial from the economic evaluation (see Section 5.3.3). In summary, this trial was well conducted and appropriate to be included in the submission. Results showed a statistical improvement in DFS but not in OS. It was reasonably represented in the submission, despite some inaccuracies.

4.2.3 NABCI (Sparano et al) study[5]

Trial summary

This study, available as an abstract only, evaluated whether outcomes were comparable when AC was given in combination followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer. A structured critical appraisal of the limited information currently available relating to this trial is attached in Appendix 6.

The data in this study has not yet been fully published, and there is insufficient data within the original reference to determine the robustness of the study design and the accuracy of the data quoted within the submission, much of which cannot be found within the published abstract.

Important trial points

Key trial points are outlined below;

- This study had four arms, two different schedules of paclitaxel and two schedules of doxetaxel. All patients received the same AC regimen.

- One of the paclitaxel regimens is the licensed dose in the UK and the other a weekly schedule.

- There were no significant differences in outcome, DFS or mortality between any group.

Docetaxel at the higher dose appeared to be associated with a higher risk of grade 3 and 4 toxicity (neutropenia) but it should be noted that neither of the dosing schedules chosen in the docetaxel arms corresponds exactly to the licensed dose in adjuvant therapy. Docetaxel is licensed at a dose of 75mg/m^2 every 3 weeks for 6 cycles whereas within this study patients received either 100mg/m^2 every 3 weeks for 4 weeks or 35 mgs/m^2 weekly for 12

weeks. According to the relevant SPCs, there does appear to be a difference in incidence of neutropenia. The incidence of neutropenia, the most commonly reported adverse reaction for docetaxel, was 54.2% (neutropenia defined as < 500 cells/mm^3).[30] This can be compared with the paclitaxel SPC report of 28% (< 500 cells/mm^3).[2]

Critique of the BMS submission

Insufficient data is presented in the original reference to fully assess the validity of this study. However, the presentation of this data included in the STA submission concurs fully with that presented in the provided reference and the relevant conference abstract. It would appear as though it has been copied verbatim from these. The additional data provided in the first section is copied from a Clinical Care Options (CCO) independent conference coverage summary and therefore cannot be verified. The latter part has been copied verbatim from the National Cancer Institute (NCI) trials registry.

Some further important omissions/inaccuracies are as follows;

- The table on p33 is incorrect as it does not show patient characteristics at baseline; it appears to show the results from NSABP B-28.[4]

- No information is provided with respect to randomisation, adequacy of follow-up, blinding etc, and no valid explanation is given as to why this may be. The statement; 'not known for NABCI E1199', is not an adequate justification for its omission.

- A simple table is presented showing a summary of adverse events from the trial. This again is taken from the un-cited data provided (i.e. it is not in the abstract), and consequently cannot be verified.

- No reference is made to trial NABCI E1199 in the interpretation of clinical evidence.

The lack of any data for follow-up etc makes any interpretation of the results unreliable. The trial seems to be largely ignored throughout the majority of the submission, although given the lack of supporting data, this would appear justified. Even so, the reasons for this should be clearly stated. Because of the obvious lack of supporting data it is very difficult to justify its subsequent inclusion in the economic analyses, especially given that they have chosen not to include the Mamounas (NSABP B-28) trial on the grounds that the dose given is outside the licensed application.[4]

4.3 Further trials, not identified in the BMS submission

The search strategy performed by the ERG additionally identified two further trials; Buzdar A U *et al* and Citron M L *et al*.[26 27] Critical Appraisals of both of these are attached as appendices 7 and 8. The Citron *et al* trial was not considered by the ERG to be a significant omission; however the ERG felt that the Buzdar *et al* trial should have been considered in the submission. Citron *et al* evaluated various paclitaxel regimens in conjunction with AC therapy, and compared two different sequential regimens with two different concurrent regimens. The trial showed that there was no difference in DFS (the primary endpoint) or OS between the concurrent and sequential schedules. With respect to DFS the effect of drug sequence was not significant, p=0.58. The effect of dose density was significant with the benefit in favour of fortnightly dosing as opposed to three weekly intervals; risk ratio 0.74 (95%CI 0.59-0.93) p=0.010. The study did not compare paclitaxel with alternative treatments or placebo and as such its omission from the submission was felt to be appropriate.

4.3.1 Buzdar A U et al[26]

Buzdar A U *et al* published preliminary data of a prospective randomised controlled trial that evaluated paclitaxel in adjuvant chemotherapy for patients with operable breast cancer. Five hundred and twenty four patients were enrolled in this trial, which is acknowledged to be a relatively small number, with 259 and 265 patients in the two respective arms.

This study was methodologically structured quite differently to the CALGB[3] and NSABP[4] trials; because all patients received the same duration of therapy the results are unlikely to be confounded by a "duration of treatment effect." The estimated HR for DFS at 48 months was 0.83 (95% CI, 0.79-0.88) for FAC alone and 0.86 (95% CI, 0.82-0.91) for Pac/FAC. The difference between the two arms was not statistically significant (p=0.09). This equated to an overall estimated reduction in risk (absolute risk reduction ARR) of 5.8% in favour of the Pac/FAC arm (HR 0.70; 95%CI, 0.47-1.07, p=0.09).

Points that suggest this trial was appropriately omitted from the submission:

1. The reason for the NSABP B-28 being omitted from the economic analysis was that the dose of paclitaxel was higher than the licensed dose. The dose in the Buzdar *et al* trial was even higher, at 250mg/m^2, hence a possible valid argument for it being omitted.
2. The results in this trial are still only classed as 'interim', which may be inappropriate for inclusion.

Points that suggest this trial should have been included in the submission:

1. The Buzdar trial is the only one that has an active comparator in the form of substituting paclitaxel initially for 4 cycles of FAC chemotherapy.
2. Although the results were interim, DFS at 4 years was not significant – a possible bias to exclusion.
3. This trial considers a different chemotherapy regimen – FAC, which, although not the licensed regimen, may still be relevant

Communication with the lead author of this trial, Aman U. Buzdar, has revealed that there has been no follow up publication because of too few additional events so far, to update the trial.[31]

4.4 Systematic reviews

Six systematic reviews were identified in the literature search performed by the ERG, which have examined clinical trials investigating the use of taxanes in early breast cancer and have provided an overview of the ongoing research in this area. Detail on each review is attached in Appendix 9; the conclusions of these reviews are summarised below.

In general, reviews of the currently published data suggest an overall survival advantage following the addition of taxanes to anthracycline adjuvant therapy for women with early breast cancer and involved lymph nodes. The most robust evidence supports the sequential addition of four cycles of paclitaxel to four cycles of AC, the substitution of six cycles of FAC with six cycles of TAC and the sequential addition of docetaxel to FEC. Evidence reviewed from trials involving dose-dense or accelerated regimens also suggests an overall survival advantage with accelerated twice-weekly AC (× 4) followed by paclitaxel (× 4), however none of the above - mentioned review articles provides any formal meta-analysis of the trial data and only two review articles provide in depth inclusion criteria therefore the validity of such conclusions must be considered with caution.

It is noteworthy that there is no clear consensus between the reviewers in the clinical implications of the current research data. One review (Appendix 9 - Trudeau et al) concluded that level-one evidence (which would support a change in standards of clinical practice) has been shown for anthracycline-taxane regimens. However another review (Appendix 9 – Piccart et al) concludes that current clinical trials ignore the biological complexity of the disease and calls for more trials which are tailored to take into account the different subsets of breast cancer, for example ER-absent, low and rich tumours. One possible explanation for

these differences is the variable inclusion criteria used by the different reviewers, with some including more than 16 published trials whilst others only two.

Overall, it is suggested that longer follow up of all current trials is required before changes in clinical practice can be implemented.

Important differences between trials which examine the effects of sequential or concomitant addition of taxanes to anthracycline-based chemotherapy (CALGB 9344 and NSABP-B-28) are highlighted in all the review articles examined. Differences in patient characteristics at inclusion, tamoxifen delivery and dosage-intensity of the paclitaxel treatment could explain the discrepancies in the results of these trials. The implications of these differences in terms of which trial offers the most robust evidence is, however, uncertain and not directly assessed by any of the included reviews.

In terms of tolerance, the reviews all conclude that when either paclitaxel or docetaxel are given sequentially after anthracycline, the rates of haematological toxicity are no higher than those seen with the preceding anthracycline cycle. However it is generally accepted that the concomitant addition of taxanes to anthracycline regimens results in a significant increase in haematological toxicity. Furthermore it is agreed that evidence from accelerated dose trials suggests an additional increase in haematological toxicity. It is suggested that the sequential schedule will most probably be favoured to the detriment of the concomitant schedule for reasons of tolerance.

If taken together, the current reviews suggest that although there is substantial evidence for statistically significant benefit in disease-free survival and overall survival following addition of taxanes to anthracycline chemotherapy, longer follow-up is needed before clinical practice can and should be altered. In fact, it is noted throughout that anthracycline-based regimens, without a taxane, remain an acceptable standard of care. Whilst the current reviews have established taxanes in this setting, future studies will need to clarify how best to use them. In addition more information on the long-term toxic effects of adjuvant taxanes is needed as the benefits of adding taxanes to therapy need to be weighed against the additional side-effects and patient inconvenience.

4.5 Review of International Guidelines submitted in part C of the BMS submission

The detail of these guidelines is attached in Appendix 10.

U.S. National Comprehensive Cancer Network (NCCN)[32] guidelines issued in 2006 suggest the use of paclitaxel in regimens such as AC ± sequential paclitaxel or AC (× 4) + sequential paclitaxel (× 4), every 2 weekly with filgrastim support if required.[32]

Both St. Gallen and the National Institute of Health (NIH) guidelines issued in 2005 and 2000 respectively,[33] [34] note that the addition of a taxane or taxane dose-dense schedules may not be more effective than AC, FEC $_{100}$ or FAC (cyclophosphamide/doxorubicin/fluorouracil) regimens and suggest there is no evidence to support the use of taxanes in node-negative breast cancer outside the settings of a clinical trial.

Guideline updates from the NCCN in 2006 now suggest an additional role for paclitaxel in trastuzumab containing regimens such as AC followed by paclitaxel plus trastuzumab and paclitaxel plus trastuzumab followed by FEC (cyclophosphamide/epirubicin/fluorouracil) plus trastuzumab for HER-2 overexpressed tumours (regardless of hormone responsiveness). However the NCCN updated guidelines for paclitaxel are considered category 2A (based on lower-level evidence including clinical experience):

NCCN Categories of Consensus:

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.
Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.
Category 2B: There is non uniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.
It is noteworthy that the primary references used in both the up to date guidelines (St. Gallen and NCCN) are the same except for one study by Romond *et al*.[35] This study is referenced in the 2006 NCCN guidelines and is most likely the basis for the updated guidelines regarding the use of paclitaxel in trastuzumab containing regimens and could explain the differences in the recommendations given by the different guidelines.

Chapter 5
Economic evaluation

5.1 Introduction

This section describes the critique of the cost-effectiveness analysis submitted by Bristol-Myers Squibb Pharmaceuticals Ltd ('the manufacturer') by the Evidence Review Group (ERG). As part of the STA process, manufacturers are expected to perform a systematic review of existing cost-effectiveness evidence for the health care technology or process being assessed. Where there is no existing evidence or the existing evidence is insufficient, manufacturers may perform their own cost-effectiveness analysis.[6 36] Thus the submission should provide an unbiased estimate of the cost-effectiveness to the NHS of the manufacturer's product, and an estimate of the associated decision uncertainty. In order to achieve this, the submission must provide unbiased estimates of the costs and effects of all relevant comparators, with costs estimated from a UK NHS and PSS perspective and health outcomes expressed in QALYs. This allows the calculation of the incremental cost-effectiveness ratio (ICERs) for each relevant comparator. The submission must also provide an estimate of the decision uncertainty, which can be achieved by conducting a probabilistic analysis and constructing cost-effectiveness acceptability curves (CEACs). The information provided by the ICERs and the CEACs can then be used to help inform the adoption decision for the health care technology or process being assessed.

The starting point for this is the critique of the manufacturer's definition of the decision problem, already reported in Chapter 3. The submission should have contained a review of existing cost-effectiveness evidence; however, the manufacturer did not perform a search for previously published studies. No justification was provided for this omission. In the absence of a formal search strategy undertaken by the manufacturer, the ERG undertook a separate search for this component. The search conducted by the ERG identified 65 records. Further details of the search strategies and databases used are shown in Appendix 10. Titles and abstracts of all records were screened; no previous cost-effectiveness analyses on the use of paclitaxel in an adjuvant setting for breast cancer were identified by the ERG. Although none of these references directly assessed the cost-effectiveness of paclitaxel in this particular context, it is possible that some of the references could contain relevant data on the costs and utility values necessary for the economic evaluation.

This chapter focuses on the economic evidence submitted by the manufacturer. The submission is reviewed on the basis of the manufacturer's report and by direct examination of the electronic model. The critical appraisal is conducted with the aid of a checklist for assessing the quality of economic evaluations[37] and a narrative review to highlight key assumptions and possible limitations.

5.2 Description of the economic model submitted by BMS

This section provides a narrative overview of the economic model provided in the manufacturer's submission. Table 5.1 provides a summary of the structure, assumptions and evidence sources used for the manufacturer's economic evaluation. A quality checklist is provided in Appendix 11. The potential limitations of the approaches used by the manufacturers are discussed in the next section (Section 5.2).

Table 5.1 Summary of manufacturer's economic evaluation

	Assumption	Source/justification	Signpost
Model	Markov state-transition model with lifetime horizon, cycle length of 1 year	None provided	Section 5.2.2 (pg 36) Figure 5.1 (pg 37)
Natural history	Equivalent to AC arm of single randomised trial. Baseline risk assumed constant after year 7 (maximum follow-up in trial).	Baseline data taken from CALGB 9344.[3] Justification for constant risk after year 7 based on Bonadonna[38] which compared CMF to no treatment, but no corresponding statements found in original paper.	Section 5.2.3 (pg 37)
Treatment effect on DFS	Lifetime treatment effect	Probability of recurrence based on CALGB 9344[3] and NABCI E1199.[5] No justification provided for lifetime treatment effect	Section 5.2.4 (pg 38) Table 5.2 (pg 40)
Treatment effect on OS	Location of recurrence based on excluded clinical trial NSABP-B28. Risk of progression following a recurrence independent of treatment received and based on a previous economic study rather than OS in included trials.	Mamounas *et al.*[4] Johnston (2001).[39] Manufacturers state belief that OS from trials would overestimate survival and would not allow recognition of costs and quality of life implications associated with progression.	Table 5.2 (pg 40) Section 5.2.3 (pg 37)
Adverse events	Only considers the costs of managing neutropenia. All febrile neutropenia is hospitalised and treated with 14 day course of G-CSF. All neutropenia assumed to occur in 1st cycle of treatment and be prevented in subsequent cycles by G-CSF. No attempt to quantify the potential impact of side-effects on quality of life.	Probability of neutropenia based on CALGB 9344[3] and NABCI E1199.[5] No justification for inclusion or exclusion of adverse events.	Section 5.2.5 (pg 39)
Health-related quality of life	External utility estimates assigned to acute-phase period and the main health states. Utility during acute phase assumed to be the same for all chemotherapies. Utility for distant recurrence assumes that it is treated with 2nd-line chemotherapy.	Abstract by Sorensen *et al.*[40] No justification provided for selection of data source.	Section 5.2.6 (pg 40) Table 5.4 (pg 48)
Treatment costs	Average patient weighs 70kg with body surface area of $1.7m^2$. Cost of 1hr chemotherapy administration assumed equal to 1 outpatient visit. Cost of additional hours required for administration adjusted on the basis of US costs.	BNF 50. No justification provided for approach used to cost administration.	Section 5.2.7 (pg 41) Table 5.5 (pg 51)
Health state costs	Primary surgery based on that received in CALGB 9344. Death due to breast cancer incurs palliative care cost but death due to other causes does not.	Johnston (2001).[39]	Section 5.2.7 (pg 41) Table 5.6 (pg 53)
Discount rates	3.5% for health outcomes and costs	In accordance with NICE guidance.[36]	

DFS = disease-free survival; OS = overall survival

In the absence of a systematic review of existing cost-effectiveness evidence by the manufacturer, their entire economic submission was based on the results of their own economic evaluation. This took the form of a Markov model developed in Microsoft Excel. The manufacturer did not report the methods used to identify primary studies to inform estimation of model parameters.

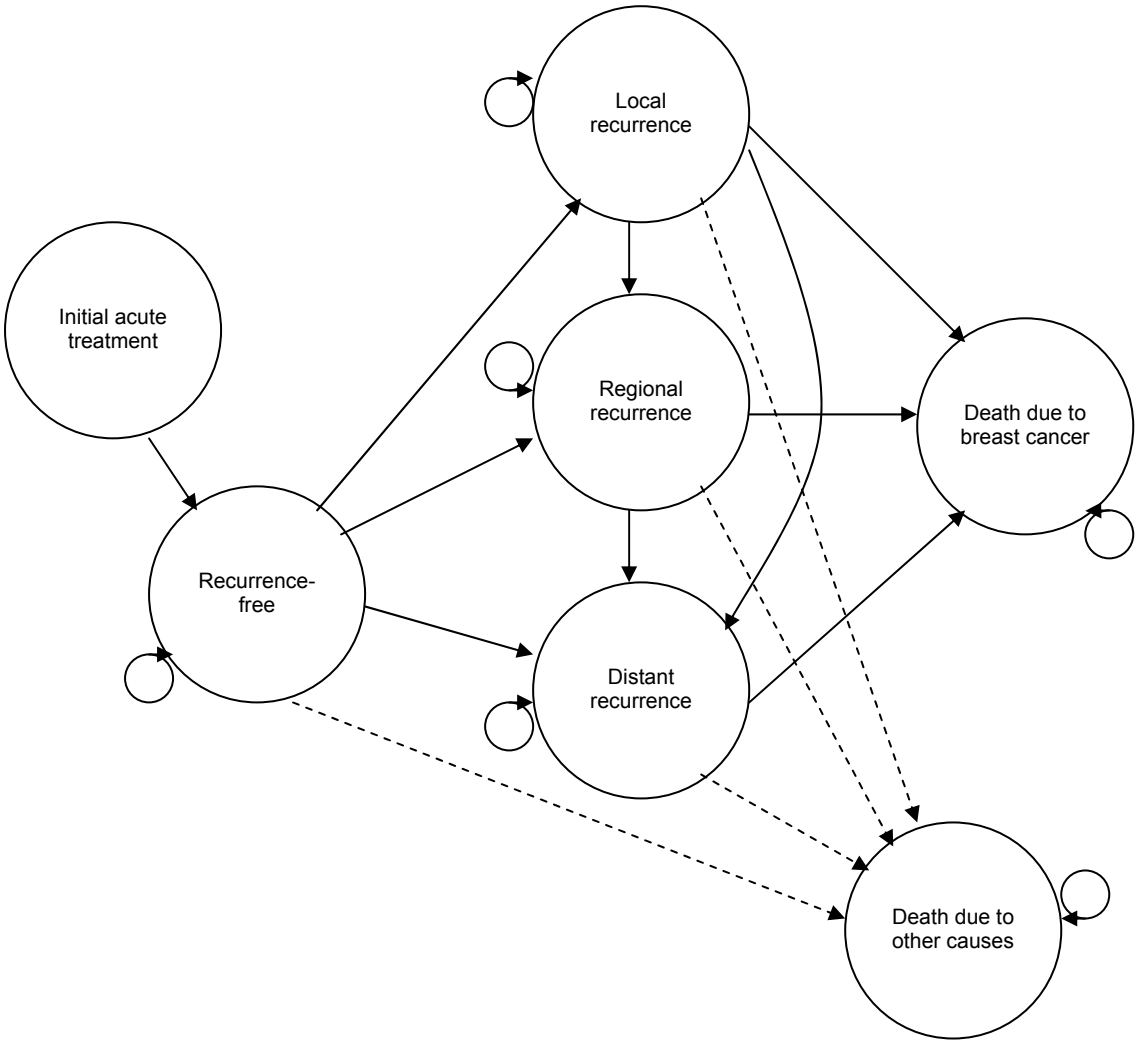
5.2.1 Comparators

The Markov model considered a hypothetical cohort of women aged 50 years with operable node positive breast cancer. The baseline in the model was treatment with standard AC therapy (doxorubicin 60mg/m^2 in combination with cyclophosphamide 600mg/m^2) every 3 weeks for 4 cycles. In the primary analysis this was compared with a treatment strategy of 4 cycles AC therapy followed by paclitaxel at the licensed dose (175mg/m^2) every 3 weeks for 4 cycles (strategy AC-P3). A secondary analysis incorporated 3 further treatment arms of 4 cycles standard AC followed by: i) paclitaxel 80mg/m^2 every week for 12 cycles (strategy AC-P1); ii) docetaxel 100mg/m^2 every 3 weeks for 4 cycles (strategy AC-D3); iii) docetaxel 35mg/m^2 every week for 12 cycles (strategy AC-D1). With the exception of 4 cycles of AC and strategy AC-P3, none of the comparators in the economic model is currently licensed for use in this way in the NHS. The manufacturer did not justify their choice of comparators.

5.2.2 Model structure

The Markov model included an initial 24 week acute phase, followed by a long-term model comprising 6 health states. During the initial 24 week period all patients were assumed to complete adjuvant chemotherapy and it was assumed that no mortality or disease progression would occur. At the end of the acute phase all patients entered the recurrence-free health state of the long-term model. From this health state, patients could progress to either local recurrence, regional recurrence, or distant recurrence. Patients who experienced a local recurrence could progress to regional or distant recurrence, or death due to breast cancer. Patients who experienced a regional recurrence could progress to distant recurrence or death due to breast cancer. Patients could progress from distant recurrence to death due to breast cancer. Patients could die from causes other than breast cancer from any state in the long-term model. The model used a cycle length of 1 year, and had an approximate lifetime horizon (40.5 cycles). Costs and health benefits were discounted at a rate of 3.5% per annum. A schematic of the model is shown in Figure 5.1.

Figure 5.1 Schematic of Markov model submitted by BMS



5.2.3 Natural history

This section provides an overview of how the manufacturer defined the baseline in their economic model. The baseline in the model considers the risk of recurrence for a woman with operable node-positive breast cancer treated with 4 cycles of AC as adjuvant chemotherapy. The risks of progression and death conditional on recurrence are assumed to be independent of treatment received.

The baseline absolute hazard for any recurrence was based on disease-free survival (DFS) in the overall AC arm of Henderson *et al*.[3] The study provided estimates of the proportion of patients remaining disease-free at 1, 2, 4 and 7 years from treatment initiation. In the absence of follow-up data beyond 7 years, the absolute hazard of any recurrence in year 7 was carried forward and assumed constant for the remaining duration of the model. The

source of data for the probability of death due to causes other than breast cancer is not reported.

Disease progression between type of recurrence and to death due to breast cancer was not based on the clinical trials used to provide evidence of effectiveness. Instead, the transition probabilities were taken from a previously published model of breast cancer screening.[39] The transition probabilities in this study were themselves based on a previously published decision-analytic model of adjuvant chemotherapy in node negative breast cancer.[41] The manufacturer's submission incorrectly states that the transition probabilities were based on patients in the Nottingham City Hospital database. As the study did not provide an estimate of the variance around the transition probabilities, the uncertainty around the mean estimates was characterised using beta distributions by arbitrarily assuming that the alpha and beta parameters summed to 100.

5.2.4 Treatment effects within the submission

This section provides an overview of how treatment effects were applied to the baseline in the economic model in order to compare each treatment strategy. Treatment is assumed to affect the risk of recurrence and the site of recurrence.

The hazard ratio for DFS was taken from Henderson *et al*[3] for AC-P3 compared to 4 cycles AC. Indirect hazard ratios for DFS were calculated for AC-P1, AC-D1 and AC-D3 based on the common comparator of AC-P3 in Sparano *et al*[5] using standard methods.[42] The model assumed that treatment effects remained constant for the duration of the model (i.e. over a patient's lifetime). The estimated hazard ratios (direct and indirect) for DFS were then applied to the baseline hazard ratio in order to estimate a specific hazard for each comparator assessed in the model. These were then converted to probabilities in the model.

The proportions of recurrences that were either local, regional or distant were taken from the AC arm of trial NSABP B-28 for standard AC therapy, and from the paclitaxel arm (dose 225mg/m^2) for all treatment strategies that included a taxane.[4] This was incorrectly referenced to Henderson *et al* in the manufacturer's submission, which states that data from NSABP B-28 were excluded from the economic model. The uncertainty around the proportion of patients experiencing each type of recurrence was modelled using a Dirichlet distribution to ensure that the total probability summed to one.[43]

In summary, the treatment effect is applied to the baseline risk of any recurrence. The location of recurrence is determined from the NSABP B-28 trial. Following a recurrence, the risks of further recurrence (disease progression) or death due to breast cancer are taken from a previously published decision-analytic model. Thus the model does not make use of the data on overall survival from the included clinical trials.[3 5]

5.2.5 Adverse events

This section provides an overview of the how the manufacturer's submission incorporates adverse events, specifically toxicity associated with chemotherapy for breast cancer. The model only includes the resource utilisation and costs associated with the management of neutropenia. The manufacturers do not provide justification for excluding all other adverse events. It is assumed that all hospitalisations were for febrile neutropenia, and that all febrile neutropenia incurs a hospitalisation. It is assumed that neutropenia occurs during the first cycle of treatment, and is prevented thereafter by treatment with a 14 day course of G-CSF.

The baseline probability of hospitalisation was calculated from the reported percentage of patients hospitalised for toxicity while receiving standard AC from Henderson *et al*.[3] A relative risk of hospitalisation on AC-P3 was then calculated based on the percentage hospitalised whilst receiving paclitaxel. The relative risks of febrile neutropenia for AC-P1, AC-D1 and AC-D3 from NABCI E1199 were calculated from the proportion of patients experiencing febrile neutropenia in each arm compared to AC-P3, and these were applied as the relative risk of hospitalisation for these treatment strategies.

The baseline probability of neutropenia was calculated from the percentage of patients experiencing infection requiring antibiotic while receiving standard AC from Henderson *et al*.[3] This was then adjusted down by the ratio of febrile neutropenia events on AC-P3 from Sparano *et al*[5] to the number of infections on AC-P3 from Henderson *et al*.[3] A relative risk of neutropenia on AC-P3 was calculated using the percentage of patients experiencing infection requiring antibiotics while receiving paclitaxel in Henderson *et al*. The relative risks of febrile neutropenia for AC-P1, AC-D1 and AC-D3 were calculated from NABCI E1199 as already described. The numbers of neutropenia events were not available in the published abstract.[5] For both hospitalisation and neutropenia, indirect relative risks against AC were calculated for AC-P1, AC-D1 and AC-D3 using the common comparator of AC-P3 and established methods.[42]

Where the proportion of patients experiencing an event was used to calculate a relative risk, the proportion was applied to the total number of patients in the relevant trial arm to calculate the number of events. An adjustment was made by adding 0.5 to each value; this adjustment is normally used for mathematical convenience when there are zero events in one arm, but that was not the case here. These data were then used to calculate the relative risk and the standard error of the log relative risk according to established methods.[44] The mean and 95% confidence intervals of the hazard ratios for DFS were available from the published trial report and abstract. By taking the natural logarithm of the hazard ratio and associated confidence limits, the standard error of the log hazard ratio was calculated using the assumption that it was normally distributed. The uncertainty around the relative risk parameters and hazard ratios was characterised using a log normal distribution. The uncertainty around the baseline probabilities of hospitalisation and neutropenia was characterised using a beta distribution. Table 5.2 shows the treatment effects applied in the model.

Table 5.2 Treatment effects applied in the manufacturer's economic model

Treatment effect	AC	AC-P3	AC-P1	AC-D3	AC-D1
Compared to AC					
Recurrence (HR)	-	0.830	0.692	0.735	0.806
G-CSF treated neutropenia (RR)	-	0.647	0.648	9.985	0.648
Hospitalising toxicity (RR)	-	0.302	0.302	4.656	0.302
Proportion of recurrences that are:					
Local	0.202	0.202	0.202	0.202	0.202
Regional	0.142	0.106	0.106	0.106	0.106
Distant	0.657	0.692	0.692	0.692	0.692

HR = hazard ratio; RR = relative risk

5.2.6 Health-related quality of life

This section describes the approach used to calculate the measure of health benefit, that is QALYs, in the manufacturer's submission. Measures of health-related quality of life (HRQoL) were not included in the clinical studies used to inform the clinical effectiveness parameters. Instead, the manufacturers made use of an alternative data source to provide utility values for the health states in the economic model.

The utility values for health states in the model were taken from a conference presentation.[40] This presentation provided estimates of utility values, derived using the standard gamble technique, for health states associated with early breast cancer among post-menopausal women. The study obtained valuations from women in the US and UK with experience of breast cancer (i.e. patient valuations). Utility values were available for disease-free, local or

regional recurrence (combined), distant recurrence treated with chemotherapy and distant recurrence treated with hormonal therapy. The manufacturers state that a search of the literature indicated that few other studies have obtained utility values for the health states in the model. However, they do not report the methods or results of this review.

The utility values for local and regional recurrences in the model were assumed to be equal to the estimate for the combined state of local or regional recurrence reported in Sorenson *et al*.[40] The utility for distant recurrence was assumed to be equal to the value elicited for distant recurrence treated with chemotherapy. The model did not include a utility decrement associated with specific chemotherapy-related toxicities. Instead, the model calculated a utility value for the initial acute treatment phase of the model based on the ratio of utility for distant recurrence treated with chemotherapy to the utility for distant recurrence treated with hormonal therapy. The reasoning behind this calculation is not given. The uncertainty around the utility estimates was characterised using a beta distribution, with the exception of utility during the acute phase which was modelled deterministically (i.e. without allowing for its uncertainty).

5.2.7 Resource use and costs

This section describes the approach used to incorporate costs in the manufacturer's economic model. The cost data can be divided into those short-term treatment costs associated with the initial acute treatment phase of the model, and the longer-term costs associated with the management of the disease and future events from disease progression.

Treatment costs

The treatment costs considered in the manufacturer's economic model include the costs of drug acquisition, the cost of administering chemotherapy, and the costs of managing adverse events (neutropenia). Not included are the pharmacy costs of preparing each chemotherapy regimen and the pre-medication costs for paclitaxel and docetaxel. The manufacturers do not provide justification for the exclusion of any categories of cost.

The price of each drug is based on published UK pricing lists.[21] The submission utilises the price of the non-proprietary form of paclitaxel, and not the price of the proprietary form Taxol®. The dose per metre squared of each drug is based on the dosage given in the included trials.[3 5] The total dose is calculated by assuming that the average woman weighs 70kg and has a body surface area of 1.7m^2. The model assumes no re-use of part-used vials.

The cost of G-CSF 500,000 units per kg is included based on the proportion of patients calculated to experience neutropenia as an adverse event. The proportion of patients requiring G-CSF is low, with the exception of patients receiving AC-D3. The source for the cost of serious toxicity (febrile neutropenia incurring a hospitalisation) is a previously published economic evaluation.[45]

Both AC and docetaxel are assumed to be given over a 1 hour infusion, and paclitaxel is assumed to require a 3 hour infusion. This is consistent with the SPC for each chemotherapy regimen. The source for the unit cost of a 'chair' for a 1 hour intravenous infusion is the cost of one outpatient visit.[39] Additional hours were assumed to incur a lower cost based on the ratio of the US Current Procedural Terminology (CPT) codes 96410 and 96412, which represent, respectively, the cost for 1 hour and additional hours of intravenous chemotherapy administration.

Health state costs in the long-term model

The long-term costs associated with management of the disease and its progression can be divided into the costs associated with the short-term costs of treating an event, for example a recurrence or a death due to breast cancer, and the long-term costs of managing patients according to the events they have experienced.

Cost data were taken from a previously published study[39] that derived cost estimates from a database at City Hospital, Nottingham, UK. These were updated to the price year 2004 using the Hospital and Community Services Pay and Prices Index, and used to calculate the follow-up costs for each health state in the long-term model. The items costed for the treatment of recurrence included investigative procedures, treatment and follow-up, as shown in Table 5.6. The source for the proportions of patients consuming each treatment item is unclear. The reference list indicates that the manufacturers also made use of information from Johnston's PhD thesis.

In addition to the cost of treating recurrence, the study provided a cost of palliative care which is applied in the model to deaths due to breast cancer. No cost is applied to death due to other causes. Following a local recurrence, patients are assumed to incur 1 clinician visit per year. Follow-up for a regional recurrence comprises 2 clinician visits and 1 mammography per year. Following a distant recurrence, patients are assumed to receive second-line chemotherapy throughout their remaining survival.

5.2.8 Sensitivity analyses

As mentioned earlier, the primary analysis focuses on the comparison of AC with AC-P3. In secondary analyses comparisons are made between AC-P3, AC-P1, AC-D3 and AC-D1. An additional analysis was presented that compared the pooled paclitaxel arms to the pooled docetaxel arms. The interpretation of this sensitivity analysis is not clear. A sensitivity analysis is included that assessed the impact of reductions in the price of paclitaxel. The manufacturers also explored the sensitivity of the model to reductions in the cost of neutropenia events, and to altering the utility value for distant recurrences. A sensitivity analysis was conducted using a discount rate of 6% per annum for costs and 1.5% per annum for health outcomes. The manufacturers acknowledge that the use of external data sources for the probability of progression and survival following a recurrence resulted in the model underestimating overall survival in comparison to the included clinical trials. A threshold analysis was conducted to reduce the risks of progression to the point where overall survival matched that in Henderson *et al*.[3] Results were presented for the time horizon varying to 5, 10 and 20 years. No sub-group analyses were conducted.

5.2.9 Model validation

The manufacturers state that disease-free survival in the model matched that in the clinical trial used to inform the model baseline. They acknowledge that the model underestimates overall survival compared to the clinical trial, which results from the use of an alternative data source to inform progression and survival. No further model validation is reported.

5.3 Critique of the approach used in the manufacturer's submission

This section provides a critical appraisal of the assumptions and methods used in the manufacturer's economic evaluation. Technical errors found in examination of the electronic model are also reported. The critical appraisal follows the same order as Section 5.2, and a summary table is provided in Appendix 12, along with potential actions that could address the concerns highlighted.

5.3.1 Description of the model

As no systematic reviews were undertaken to inform any of the model parameters, this would imply that the manufacturers made selective use of the available data. The possible existence of additional or alternative data sources for all the model parameters increases the uncertainty in the validity of the model results.

The choice of comparator for the economic analysis is not justified and appears flawed. The licensed indication for paclitaxel states that it should be viewed as an alternative to extended AC therapy. Consultation with clinical experts indicated that 4 cycles of AC would not be standard treatment in the NHS among women considered sufficiently high-risk enough to require treatment with a taxane. No comparison was made with extended AC (6 cycles), the licensed use of docetaxel or other standard anthracycline-containing regimens such as FAC or FEC, all of which may be relevant in this patient population. In addition, there exists a generic alternative to Taxol® that is a direct comparator because, although probably not clinically different from the proprietary version, its acquisition cost may differ.

The structure of the economic model appears to be appropriate for the decision problem. The time horizon, discount rates used and probabilistic nature of the model conform to NICE methods guidelines for economic evaluations.[36] A comparison of the manufacturer's model with the NICE Reference Case is provided in Table 5.3.

Table 5.3. Comparison of manufacturer's submission with NICE Reference Case

Element of assessment	Reference case	Manufacturers submission
Defining the decision problem	N/A for STA	Treatment of interest was the licensed form of paclitaxel. Model considers a hypothetical cohort of women aged 50 years with operable node-positive breast cancer (based on patients recruited to Henderson *et al*[3]).
Comparator	Alternative therapies routinely used in the NHS	**No**. 4 cycles AC is used as the comparator. This is unlikely to represent standard treatment in the UK for this high-risk patient population.
Perspective on costs	NHS and PSS	**Yes**. However, some relevant categories of cost are omitted from the analysis (e.g. pre-medication).
Perspective on outcomes	All health effects on individuals	**Yes**. However, model does not include differential utility impact related to toxicity while receiving treatment.
Types of economic evaluation	Cost-effectiveness analysis	**Yes**.
Synthesis of evidence on outcomes	Based on a systematic review	**No**.
Measure of health benefits	Quality-adjusted Life Years (QALYs)	**Yes**.
Description of health states for calculation of QALYs	Health states described using a standardised and validated generic instrument	**No**. Utilities based on standard gamble methodology. Health state descriptions not publicly available.
Methods of preference elicitation for health state valuation	Choice-based method, for example, time trade-off, standard gamble (not rating scale)	**Yes**.
Source of preference data	Representative sample of the public	**No**. Sample consisted of patients: 67 postmenopausal women aged 55-70 years in the UK (23) and USA (44) and who had a history of stage 1 or 2 operable early breast cancer.
Discount rate	An annual rate of 3.5% on both costs and health effects	**Yes**.
Equity provision	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	**Yes**.

5.3.2 Natural history

The data used for the risk of recurrence were based on patients recruited to a clinical trial in North America. These baseline risks are likely to be appropriate for application to a decision model in the context of the UK. However, the use of an average risk from a clinical trial population may conceal variation between important sub-groups which differ in terms of their prognostic factors and baseline risk of future events. The use of the external source of data for risks of further events following a recurrence was viewed as acceptable by clinical experts. The failure to report the source for the risk of death due to other causes is a limitation of the manufacturer's report.

5.3.3 Treatment effects

The treatment effects on DFS appear to have been used appropriately in the economic model. However, those treatment effects were based on selective use of the available evidence and may therefore incorporate selection bias. Given that the manufacturer's include NABCI E1199 in a secondary analysis, it appears inconsistent to have not also considered NSABP B-28, which was included in their review of clinical effectiveness, or Buzdar *et al*, which was omitted from their review of clinical effectiveness. All three trials included unlicensed comparators. Given the similarity of the treatment effects on DFS reported in these omitted trials, it is unlikely that the conclusions of the economic model would be significantly altered by their inclusion. However, they may have contributed useful additional safety data.

The assumption that treatment effects on recurrence last for a lifetime is made with little supportive evidence. At the very least, the implications of this assumption could have been explored in a sensitivity analysis. Consultation with clinical experts indicated that they would not expect the site of recurrence to differ by treatment, and so this assumption in the model potentially propagates random variation in the site of recurrence through the model. In addition, the source of data for the site of recurrence was a clinical trial that the manufacturer had chosen to exclude from the economic analysis. The data were incorrectly referenced to Henderson *et al,*[3] and the correct source[4] was identified during the review by the ERG. An error in defining the Dirichlet distribution used to describe the uncertainty around the proportion of recurrences that were local, regional and distant caused the proportion of patients experiencing regional and distant recurrences to be higher than that implied by the data for patients receiving AC. As a result, the probabilistic analysis of the manufacturer's model incorporates a bias in favour of the AC-taxane arms.

5.3.4 Adverse events

The inclusion of only neutropenia as an adverse event was felt to be appropriate from a resource use point of view. The clinical experts felt that other adverse events could differ between AC and taxanes, for example nail bed changes and fluid retention, but that these would not require active treatment beyond dose adjustments. However, these issues may be important when considering HRQoL while on treatment.

The data used to calculate the relative risks of hospitalisation and neutropenia for AC-P3 compared to 4 cycles AC did not allow such a calculation. The published trial paper reported the number of infections or hospitalisations while receiving AC, and the number of hospitalisations or infections while receiving paclitaxel. The number of infections or hospitalisations while receiving paclitaxel is not equivalent to the number that would be experienced while receiving strategy AC-P3, as they exclude any adverse events experienced while receiving the first 4 cycles of AC. Fewer events were reported while patients received paclitaxel compared to the period for which they received AC. However, *a priori* we would expect patients receiving strategy AC-P3 to experience the same number of events while receiving AC as those who received 4 cycles of AC without paclitaxel. The manufacturer's calculation does not account for these events and therefore calculates a relative risk reduction for AC-P3 compared to AC. Clearly if any events occur while receiving paclitaxel the overall comparison should indicate a relative risk increase associated with 4 additional cycles of chemotherapy. The 'relative risk reductions' applied in the electronic model were therefore incorrect and biased in favour of AC-P3. The indirect relative risks calculated for AC-P1, AC-D3 and AC-D1 also incorporate the bias in favour of taxane therapy caused by the incorrect calculation of the relative risk for AC-P3 compared to AC.

The method used to calculate the uncertainty around the relative risks for hospitalisation and neutropenia assumes that all patients randomised in the trial were included in the analysis. This assumption would underestimate uncertainty in the presence of censoring. The addition of 0.5 to the numbers of events was not necessary, but is unlikely to impact the results.

The manufacturer did not provide evidence to support their assumption that all hospitalisations in CALBG 9344 were for febrile neutropenia. In addition, they failed to justify their downward adjustment of the baseline rate of infections from CALBG 9344. It is likely that some of the assumptions were the result of poor reporting of toxicity data in the included clinical trials. Data in the manufacturer's submission indicate that it would have been possible to calculate separate relative risks for neutropenia and febrile neutropenia from

NABCI E1199 (see Table 11 in submission).[1] An alternative to the assumptions used in generating the relative risks for AC-P3 compared to AC for neutropenia from Henderson *et al* would have been to use the data reported on granulocytopenia (grade 4) and infection (grades 3 and 4), provided in Table 10 of the manufacturer's submission.[1] While these do not directly represent the events being modelled, the data would facilitate a more appropriate calculation of a relative risk.

5.3.5 Health-related quality of life

The approach used to calculate QALYs by applying utility values to the health states in the economic model is appropriate. However, the calculation of the utility value for the initial acute treatment phase appears to have no supportive evidence. Quality of life while receiving chemotherapy could feasibly differ between regimens, and this is not considered in the manufacturer's submission.

The distributional parameters (alpha and beta) used to describe the uncertainty around the utility estimates in the manufacturer's economic model did not match those which the ERG estimated using data reported in the submission. The values applied in the manufacturer's electronic model imply a much lower standard deviation than the estimates reported in the submission itself. The utility values used in the economic model are shown in Table 5.4. The utility value estimated for the disease-free health state appears relatively high at 0.974, and no attempt was made to reflect any decline in general health of the population as the hypothetical cohort ages. For comparative purposes the UK population norm, based on EQ-5D scores, for females aged 45-54 is 0.85, decreasing to 0.71 for females aged 75 and over.[46] By using a single utility estimate for the disease-free state throughout the model the manufacturer's estimates of the incremental QALYs associated with the taxane regimens are likely to be overly optimistic.

Table 5.4. Utility values applied to health states in the manufacturer's submission

Health state	Mean	Standard deviation in economic model*	Standard deviation reported in submission
Acute treatment period	0.597	None	None
Disease-free	0.974	0.000016	0.01
Local recurrence	0.816	0.000889	0.24
Regional recurrence	(same as local)		
Distant recurrence (chemotherapy)	0.432	0.002293	0.24
Distant recurrence (hormonal therapy)**	0.724	None	0.29

* calculated as $\alpha\beta/((\alpha+\beta)^2(\alpha+\beta+1))$ where α and β represent the alpha and beta parameters of the beta distribution applied in the economic model

** used in sensitivity analysis

By using a beta distribution to characterise the uncertainty around the utility values, the model does not allow the utility for any health state to be negative. This is probably a reasonable approximation, even though the standard deviation around the utility value for a distant recurrence treated with chemotherapy indicate that it could become marginally negative for some simulations if modelled using an alternative distribution.

5.3.6 Resource use and treatment costs

The submission makes use of the unit cost of non-proprietary paclitaxel; £1009.80 per cycle of 175mg/m^2 for a body surface area of 1.7m^2. This would be appropriate if the intervention being assessed were generic paclitaxel and not the manufacturer's product. However, throughout the manufacturer's submission they refer to paclitaxel as Taxol®, and so this unit cost is inappropriate. For comparison, the unit cost of Taxol® is £1043.46 per cycle of 175mg/m^2 for a body surface area of 1.7m^2. The exclusion of the pre-medication costs associated with paclitaxel and docetaxel is not justified in the submission. The SPC for paclitaxel (http://emc.medicines.org.uk accessed 14/02/06) indicates that pre-medication for paclitaxel should be given by intravenous infusion. While the acquisition costs of the pre-medication drugs is relatively low (approximately £3.80 per cycle), the infusion would incur an additional 30-60mins of administration time. The use of the cost of one outpatient visit to represent 1 hour of chemotherapy administration is not appropriate. It is likely that the cost of one outpatient visit represents the average cost per visit, averaging over the length of all visits. As such, the validity of adjusting this average cost by the ratio of first to subsequent hours based on US CPT codes is unclear.

A number of technical errors were noted by the ERG in the calculation of treatment costs. The unit cost for 100mg/m^2 docetaxel was entered incorrectly (£1009.80 instead of £1232.25 calculable from BNF 50). For all regimens doxorubicin was priced at 50mg/m^2 rather than 60mg/m^2. The model also appears to contain an important error whereby the cost of administrating the first 4 cycles of AC in any of the AC-taxane treatment arms is omitted. For example, the cost of administration for AC-P3 is simply that of 4x3hr infusions (£800), whereas it should additionally include 4x1hr infusions (£364) for the preceding doses of AC. Since these have been added to the AC comparator assessed in the model, these should also be added to the costs of the AC-taxane treatments. The regimen costs applied in the manufacturer's economic model are shown in Table 5.5. The table also provides the regimen costs corrected for the errors noted above, the cost of pre-medication and (for illustrative purposes only) the cost of other potentially relevant comparators.

The submission made use of resource use and unit cost data that are appropriate from a UK NHS perspective. However, insufficient detail was provided in the manufacturer's submission to enable proper validation of the health state costs applied in the economic model. The total cost for each event is lower than the estimates in the previously published study.[39] This may be due in part to the proportion of patients assumed to receive primary mastectomy in the model (0.7) differing to that used in Johnston (not reported), and also due to the fact that the unadjusted costs appear to be just over 4% lower than those available in the published paper. While costs were applied to death due to breast cancer, costs were not assigned to death due to other causes. This differentiation is not justified, and may incorporate a bias toward deaths due to other causes if these are also expected to incur costs. Table 5.6 provides detail of the items of resource use used in calculating the health states costs in the manufacturer's economic model.

The simplifying assumption that patients experiencing a distant recurrence receive second-line chemotherapy for the duration of their survival is probably justifiable. Given the high probability of death following a distant recurrence (0.745), the average remaining survival period is in the region of 8-9 months (if an exponential distribution is assumed).

Table 5.5 Regimen costs used in manufacturers submission, corrected regimen costs and additional regimen costs for comparison (based on average woman weighing 70kg with a body surface area of 1.7m^2)

	Model drug cost	Model administration cost	Number of cycles	Regimen total*	Corrected regimen total**	Pre-medication costs *(per cycle)*
AC						
Doxorubicin 60mg/m^2	£185.40	£90.89	4	£1,196	**£1,361**	n/a
Cyclophosphamide 600mg/m^2	£7.92					
AC-P3 *(AC as above)*						
Paclitaxel 175mg/m^2	£1,009.80	£199.95	4 AC then 4 P3	£5,651	**£6,238**	£3.80+£90.89
AC-P1 *(AC as above)*						
Paclitaxel 80mg/m^2	£561.00	£90.89	4 AC then 4 P1	£8,653	**£9,241**	£3.80+£90.89
AC-D3 *(AC as above)*						
Docetaxel 100mg/m^2	£1,009.80	£90.89	4 AC then 4 D3	£5,767	**£7,245**	£7.68
AC-D1 *(AC as above)*						
Docetaxel 35mg/m^2	£488.25	£90.89	4 AC then 4 D1	£7,780	**£8,368**	£7.68
Other regimens	**Drug cost**	**Administration cost** *(based on model)*	**Number of cycles**		**Regimen total***	**Pre-medication costs** *(per cycle)*
oral-CMF						
Cyclophosphamide 100mg/m^2	£0.42	£90.89	12		**£1,760**	n/a
Methotrexate 40mg/m^2	£5.24					
Fluorouracil 600mg/m^2	£16.00					
FAC						
Fluorouracil 500mg/m^2	£12.80	£90.89	6		**£1,969**	n/a
Doxorubicin 50mg/m^2	£185.40					
Cyclophosphamide 500mg/m^2	£5.04					
FEC						
Fluorouracil 500mg/m^2	£12.80	£90.89	6		**£2,942**	n/a
Epirubicin 100mg/m^2	£328.24					
Cyclophosphamide 500mg/m^2	£5.04					
E-CMF						
Epirubicin 100mg/m^2	£328.24	£90.89	4 E then 4 CMF		**£2,409**	n/a

Cyclophosphamide 750mg/m^2	£2.76					
Methotrexate 50mg/m^2	£5.24					
Fluorouracil 600mg/m^2	£16.00					
TAC						
Docetaxel 75mg/m^2	£1.023.00	£181.78	6		**£9,901**	£7.68
Doxorubicin 50mg/m^2	£185.40					
Cyclophosphamide 500mg/m^2	£5.04					

* sum of administration and drug costs multiplied by the number of cycles required to complete a course of therapy

** corrected for mistake in administration cost, dosage of doxorubicin and unit cost of docetaxel

Table 5.6. Comparison of cost data used in manufacturer's submission to estimates in Johnston 2001[39]

Item	Johnston *et al*[39]	Submission (unadjusted)	Submission (adjusted to 2004 @1.2801)
Treatment			
Mastectomy	£2539 £2461 (lumpectomy) £2515 (subcutaneous)	£2433	£3114
Open biopsy	£873	£837.07	£1072
Radiotherapy	£1331 (50Gy, 25#) £868 (45Gy, 15#)	£1276 £832	£1633 £1065
Chemotherapy for local or regional recurrence	NA	£899	£1151
Chemotherapy for distant recurrence	£2015 (first-line) £4336 (second-line)	£1931.08 £4156.25	£2472 £5320
Investigations			
Core biopsy	£94	£90.16	£115
Bone scan	£83	£79.2	£101
Liver ultrasound	£21	£20.15	£26
CT scan	£73	£69.5	£89
Chest X-ray	£16	£15.33	£20
Biochemistry tests	£7	£6.7	£9
Skeletal survey	£27	£26	£33
Blood count	£5	£4.4	£6
MRI	£44	£5	£6
Follow-up			
Clinician visit	£71	£71	£91
Mammography	£163 (incl. 2 outpatient visits)	£100	£128
Palliative care (death due to breast cancer)	£2750	£2750	£3520
Health states (calculated as a function of proportion receiving items listed above)			
Local recurrence	£2502		£1754
Regional recurrence	£3327		£1463
Distant recurrence	£5249		£5132
Serious toxicity	NA	£2470 + £907 + £42	£4188

5.3.7 Sensitivity analyses

The inclusion of a sensitivity analysis around the discount rates used is appropriate. However, a mistake in this analysis meant that both costs and health outcomes were in fact discounted at 1.5% per annum when costs should have been discounted at 6%. The justification and interpretation of many of the other sensitivity analyses is unclear.

The lack of sub-group analyses may limit the generalisability of the model results. The baseline risk of progression varies among patients recruited to the clinical trials according to prognostic factors such as the number of involved nodes, tumour size, patient age and whether the tumour is oestrogen-receptor positive. In addition, some studies have suggested that the treatment effect could differ according to these prognostic factors and there has been the suggestion that concurrent rather than sequential use of tamoxifen may represent a confounder. By failing to consider these issues, the average results of the economic model could potentially conceal wide variation between sub-groups in the cost-effectiveness of paclitaxel. In Section 6.1 the impact of different patient characteristics on prognosis is considered using the web-based decision aid Adjuvant! Online.

5.4 Results included in the manufacturer's submission

The submission presented the ICERs based on the deterministic model results. Table 5.7 provides a summary of the results from the manufacturer's submission.

Table 5.7 Results of the economic model reported in the manufacturer's submission

	Comparator				
Analysis	**AC**	**AC-P1**	**AC-P3**	**AC-D1**	**AC-D3**
Base-case					
Total cost	£11,080	£17,080	£14,712	£16,740	£16,227
QALYs	9.33	10.95	10.10	10.24	10.67
ICER vs AC	-	£3,713	£4,726	£6,235	£3,841
95% CI:					
lower limit	-	£1,270	£1,188	£1,561	£1,184
upper limit	-	£4,903	£3,904	£9,040	£5,517
ICERs for sensitivity analyses					
Percentage of paclitaxel acquisition cost					
75%		Dominates D3			£4,418 vs P3
50%		Dominates D3			£6,185 vs P3
25%		Dominates D3			£7,952 vs P3
Percentage of neutropenia related treatment costs					
75%		£5,589 vs D3			£1,430 vs P3
50%		£7,845 vs D3			£330 vs P3
25%		£9,860 vs D3			Dominates P3
0%		11.632 vs D3			Dominates P3
Percentage of probability of death from any recurrence					
90%		£3,063 vs D3			£2,621 vs P3
80%		£3,210 vs D3	£4,700 vs AC		£2,778 vs P3
70%		£2,980 vs D3			£2,534 vs P3
60%		£2,917 vs D3			£2,468 vs P3
Time horizon for model					
5 years		£40,252 vs D3			£32,579 vs P3
10 years		£11,424 vs D3	£21,505 vs AC		£9,253 vs P3
20 years		£4,573 vs D3			£3,795 vs P3
Utility for distant recurrence					
0.724		£3,154 vs D3			£2,704 vs P3
0.578		£3,122 vs D3			£2,677 vs P3
Discounting					
0%		£1,609 vs D3			£1,416 vs P3
6% and 1.5%		£2,152 vs D3			£1,869 vs P3

QALYs = quality-adjusted life-years; ICERs = incremental cost-effectiveness ratios; CI = confidence interval

The manufacturer concludes that their model shows robust cost-effectiveness for paclitaxel in the adjuvant treatment of early breast cancer.

5.5 Validity of the results presented in the submission

The presentation of deterministic results is not appropriate when using a non-linear probabilistic model. The confidence intervals around ICERs were calculated by taking the 2.5th and 97.5th percentiles of the ICERs generated in the probabilistic analysis. This method is not normally used to generate confidence intervals for ICERs due to the mis-interpretation of negative ICERs (which may represent either a more effective cost-saving

intervention, or a less effective more costly intervention) and the fact that the ICER, as a ratio, can exhibit an unusual distribution. It appears that there were no negative ICERs in the probabilistic results. However, due to the error in specifying the Dirichlet distribution describing the site of recurrence, which causes the probabilistic results to be biased in favour of the AC-taxane arms, the confidence interval around the ICER for AC-P3 compared to AC does not contain the mean deterministic ICER. The most appropriate way to present uncertainty in the cost-effectiveness results is by using probabilities derived from a CEAC.

Little data are presented of the effect of the sensitivity analyses on the manufacturer's primary comparison of interest (AC-P3 vs AC). Instead, the results of the sensitivity analyses concentrate on seemingly arbitrary pairings of included comparators (AC-P1 vs AC-D3 and AC-D3 vs AC-P3).

All of the results reported in the manufacturer's submission incorporate a number of technical errors that bias the economic model in favour of the AC-taxane treatment arms.

5.6 Summary of uncertainties and issues

The manufacturer's submission contains minimal description of the data sources and justification for the assumptions used for the electronic model. Additionally some model parameters were mis-referenced or based on data that are not publicly available. An electronic copy of the model was provided, which allowed a more detailed assessment of the model structure and the value of model parameters. The overall model structure appears to be appropriate for the decision problem. However, a number of issues compromise the validity of the model results:

i) the failure to conduct a systematic review for any model parameters;
ii) the inclusion of a weak comparator to represent standard therapy in the UK NHS;
iii) the failure to explore sub-groups within the overall patient population;
iv) and a number of technical errors in executing the model.

Table 5.3 compares the manufacturer's submission with the requirements of the NICE Reference Case. Without a systematic review it is impossible to know how reflective the model is of currently available data, or what potential bias the model results incorporate as a result of excluding potentially relevant data. If 4 cycles of AC are viewed as inferior to 6 cycles of AC or a 5-fluorouracil containing regimen such as FEC, then the submission may overestimate the cost-effectiveness of paclitaxel to the NHS. Docetaxel can be used in place of paclitaxel for the same indication, but the submission does not provide a

comparison with the licensed dose of docetaxel. The unlicensed regimens it does include appear to be superior to the licensed form of paclitaxel.

Chapter 6
Additional work undertaken by the ERG

This section outlines additional analyses that have been undertaken by the ERG to provide further information on areas that the ERG considered were not sufficiently dealt with in manufacturer's submission. In future STA reports, it is expected that the manufacturer would be given the opportunity to address any limitations and perform additional analyses. The manufacturer would have the opportunity to make alterations to all areas of the submission, and thus could potentially provide revised analyses that address any limitations identified by the ERG during the course of the review process. However, given that this was a pilot STA, the processes were not in place to give the manufacturer this opportunity. In this situation the ERG considered that it was important to attempt to address some of the limitations noted in the previous sections. The additional work undertaken by the ERG is intended to provide additional information on the qualitative impact of identified limitations. Given the restricted nature of these additional analyses only 3 areas are considered:

- Sub-group analysis
- Sensitivity analysis
- Additional comparator

It should be noted that the analyses into these areas are selective, and that the revised economic analyses have been undertaken to examine the robustness of the manufacturer's own model to alternative assumptions. These analyses are clearly subject to the same major limitations outlined previously concerning the lack of a systematic review component relating to both the clinical effectiveness data and the parameters in the economic model, and the fact that the comparator, 4 cycles AC, is not felt to represent current practice in the UK. The results should, therefore, only be taken as indicative of the potential impact of these gaps in the manufacturer's submission.

6.1 Sub-group analysis

As outlined in Section 5.2.8 the manufacturer's submission does not include any sub-group analysis. This section attempts to highlight the potential impact of different patient characteristics on both disease free survival (DFS), and on the improvement in outcomes from different treatment options.

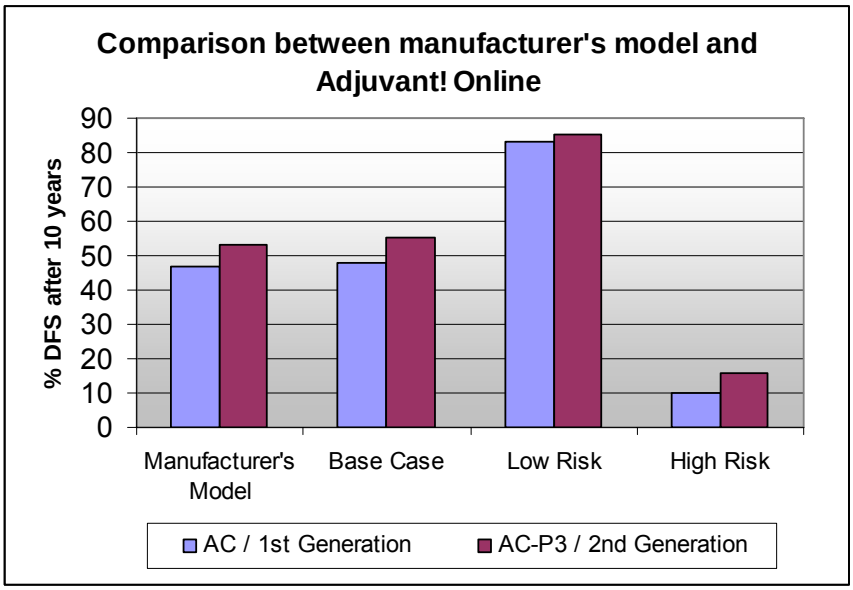
Adjuvant! Online is a web-based decision aid that predicts 10-year breast cancer outcomes with and without adjuvant therapy (see Section 3.3). It is in common use amongst clinicians, and can be used to predict the outcomes associated with different patient characteristics.[18 19] In Table 6.1, 10 year disease free survival rates from the manufacturer's model are compared with 10 year disease free survival rates from Adjuvant! Online. In the table, the 'base-case' defined by the ERG represents a set of characteristics closest to the averages from the trials used in the manufacturer's model. The next four analyses involve individually setting key prognostic characteristics of ER status, tumour grade and size, and number of positive lymph nodes, to their worst status in Adjuvant! Online. Finally a set of low-risk and high-risk characteristics are tested. (Appendix 13 gives details of the base-case, low-risk and high-risk patient characteristics entered into Adjuvant! Online.)

Table 6.1 Percentage of patients without recurrence after 10 years: comparison of manufacturer's model and Adjuvant! Online

		AC / 1st Generation	AC-P3 / 2nd Generation	Percentage point difference between treatments
Manufacturer's model		47	53	6
Adjuvant! Online	ERG base-case	48.1	55.2	7.1
	ER status negative	39.9	47.5	7.6
	Grade 3	41.9	49.4	7.5
	Size > 5.0cm	35.7	43.5	7.8
	> 9 Positive nodes	31.2	39.1	7.9
	Low-risk	82.9	85.3	2.4
	High-risk	9.8	15.7	5.9

Figure 6.1 summarises the outcomes for the manufacturer's model, and the base-case, low-risk and high-risk scenarios entered into Adjuvant! Online.

Figure 6.1 Percentage of patients without recurrence after 10 years: comparison of manufacturer's model and Adjuvant! Online



These comparisons show that, although the 10 year DFS outcomes from the manufacturer's model are broadly in line with outcomes for a set of average patient characteristics in Adjuvant! Online, changes to patient characteristics can have a very large impact on patient prognosis. There are more than 70 percentage points between the DFS in the low-risk group and the DFS in the high-risk group. Changes in these key prognostic characteristics can also have a considerable impact on the benefits gained from using a '2nd Generation' treatment regimen such as AC-P3 instead of a '1st Generation' treatment regimen such as AC. In the base-case, there is 7.1 percentage point increase in DFS from 1st Generation to 2nd Generation, whilst in the low-risk group the increase is only 2.4, and in the high-risk group the increase is 5.9. Figure 6.1 appears to indicate that the 'average' patient in the manufacturer's electronic lies somewhere between high- and low-risk, and can be expected to experience a greater absolute increase in DFS in comparison with higher- or lower-risk groups.

6.2 Sensitivity analysis

The ERG explored the impact of correcting some of the technical errors identified earlier in this critique, and testing some of the assumptions underpinning the model. Table 6.2 details the analyses undertaken:

Table 6.2 Details of errors and key assumptions in the manufacturer's submission and how these are adjusted in the sensitivity analysis

	Elements	***Position in manufacturer analysis***	***Changes made by ERG***
1.	Spreadsheet error	Spreadsheet error in specification of the dirichlet distribution used to calculate the proportion of recurrences being local, regional or distant in the AC treatment arm. Impacts results only when the model is run in stochastic mode. *Details: In worksheet "data", cells I63:I65, the proportion in each cell should be calculated by dividing by the sum of H63:H65, however where the formula has been copied down division is incorrectly by H64:H66 in cell I64 and by H65:H67 in cell I65.*	Error corrected
2.	Cost calculations	There are a number of costs that appear to have been omitted from the manufacturer's analysis: a) There are several costs resulting from giving 4 cycles of AC that should be included in the costs of the taxane arms that were excluded from the manufacturer's analysis: - Cost of G-CSF - Cost of administration - Cost of hospitalisation b) The model uses a doxorubicin dose of 50mg/m^2 for cost calculations, whilst the standard dose, and the dose used in the referenced trials, is 60mg/m^2 c) The model mistakenly uses the cost of a dose of paclitaxel for the cost of a 100mg/m^2 dose of docetaxel in the 3-weekly docetaxel arm.	a) The additional costs resulting from the initial 4 cycles of AC have been added to the taxane treatment arms b) The cost of doxorubicin has been recalculated for a 60mg/m^2 dose. c) The correct cost for a 100mg/m^2 docetaxel is used.
3.	Relative treatment effect	Relative treatment effects are assumed to continue for the lifetime of the model	Relative treatment effects are only assumed to apply for 7 years - the length of follow-up in Henderson *et al*.[3]
4.	Location of recurrence	Different proportions for whether a recurrence is local, regional or distant are assumed for the AC arm to all other arms	Proportions for location of recurrence in the AC arm are set to be the same as for the other treatment arms

The stochastic results obtained for the primary analysis of AC against AC-P3 are shown in table 6.3.

Table 6.3. Stochastic results of the sensitivity analyses for AC against AC-P3

Analysis	Treatment Arm	Cost	QALY	ICER	Probability cost effective for maximum WTP:		
					£10,000	£20,000	£30,000
Results reported in manufacturer's submission	AC-P3	£14,712	10.10	4,726	NA	NA	NA
	AC	£11,080	9.33		NA	NA	NA
1: Correction of spreadsheet error	AC-P3	£14,753	10.15	4,651	0.72	0.86	0.89
	AC	£11,137	9.37		0.28	0.14	0.11
2: Corrections for spreadsheet error and costs.	AC-P3	£15,671	10.14	5,810	0.66	0.85	0.89
	AC	£11,194	9.37		0.34	0.15	0.11
3: Corrections plus no differential treatment effect beyond 7yrs	AC-P3	£16,075	9.80	11,331	0.27	0.67	0.78
	AC	£11,280	9.37		0.73	0.33	0.22
4: Corrections plus no differential recurrence location between arms	AC-P3	£15,709	10.16	5,488	0.68	0.84	0.89
	AC	£11,342	9.36		0.32	0.16	0.11

The deterministic ICER presented in the manufacturers report was £4,726. Correcting for the spreadsheet error produces an ICER very close to this deterministic result in contrast to the stochastic ICER of £2,307 produced by the manufacturer's model. In addition, correcting for the identified errors in cost calculations leads to an increase in the ICER of AC-P3 against AC by just over £1,000 to £5,810 per QALY. After making these corrections, the model gives the probability of AC-P3 being cost-effective at a cost-effectiveness threshold of between £20-£30,000 per QALY, to be in the range 85-89%.

The analysis that has the greatest impact on the ICER is the assumption of no differential treatment effect beyond 7 years, as opposed to the assumption in the manufacturer's analysis of lifetime differential treatment effect. This results in an increase in ICER of over £5,000 to £11,331 per QALY.

The analysis of assuming no difference in the site of recurrence (local, regional or distant) between treatment arms has little impact on the ICER. If anything, the manufacturer's assumption shows a slight bias towards AC.

Table 6.4 presents analysis results based on all treatment options.

Table 6.4. Stochastic results of the sensitivity analyses for all treatment regimens

Analysis*	Treatment Arm	Cost	QALY	ICER	Probability cost effective for maximum WTP:		
					£10,000	£20,000	£30,000
1: Correction of spreadsheet error	AC	£11,137	9.37		0.00	0.00	0.00
	AC-P1	£17,125	10.98	3717	0.52	0.56	0.57
	AC-P3	£14,753	10.15	ED	0.06	0.03	0.03
	AC-D1	£16,808	10.26	D	0.11	0.11	0.11
	AC-D3	£16,379	10.69	ED	0.31	0.30	0.30
2: Correction of spreadsheet error and costs	AC	£11,194	9.37		0.00	0.00	0.00
	AC-P1	£18,045	10.99	4228	0.55	0.58	0.58
	AC-P3	£15,671	10.14	ED	0.06	0.03	0.03
	AC-D1	£17,729	10.26	ED	0.09	0.09	0.09
	AC-D3	£18,213	10.73	D	0.30	0.30	0.30
3: Corrections plus no differential treatment effect assumed beyond 7yrs	AC	£11,280	9.37		0.09	0.00	0.00
	AC-P1	£18,824	10.25	8642	0.46	0.54	0.55
	AC-P3	£16,075	9.80	ED	0.13	0.08	0.06
	AC-D1	£18,187	9.85	ED	0.10	0.11	0.11
	AC-D3	£18,896	10.10	D	0.23	0.27	0.28
4: Corrections plus no differential recurrence location between arms assumed	AC	£11,342	9.36		0.00	0.00	0.00
	AC-P1	£18,121	10.96	4258	0.51	0.54	0.55
	AC-P3	£15,709	10.16	ED	0.07	0.03	0.03
	AC-D1	£17,777	10.25	ED	0.11	0.10	0.10
	AC-D3	£18,268	10.74	D	0.31	0.33	0.33

D = Dominated, ED = Extended Dominated

**see table 5.7 for results reported in manufacturer's submission*

After correcting for the described errors, and when considering all treatment options, AC-P1 was shown to be cost-effective against AC at an ICER of £4,228. All other treatment regimens, including AC-P3, were dominated or ruled out be extended dominance in the comparison. For a cost-effectiveness threshold of between £20-£30,000 per QALY, the model gives the probability of the different treatment options being cost effective to be 0% for AC, 58% for AC-P1, 3% for AC-P3, 9% for AC-D1, and 30% for AC-D3. Therefore, the regimen under review – AC-P3 – appears to be the least likely of all the taxane regimens to be cost-effective at this threshold.

6.3 Additional comparator

The regimens AC-P1, AC-D1 and AC-D3 considered in the manufacturer's economic model are not currently licensed for use in this way in the UK NHS. However, there is a licensed docetaxel regimen, known as TAC, which is a relevant taxane comparator for the AC-P3

regimen. This regimen involves giving docetaxel, doxorubicin and cyclophosphamide every 21 days for 6 cycles.

An indicative analysis has been conducted by the ERG, using the manufacturer's model, to compare AC, AC-P3 and TAC. Care should be taken in interpreting this analysis as it has not been possible to link in this comparator using robust methodology. The licensed docetaxel arm was based on the AC-D3 arm of the manufacturer's model, after making the corrections detailed in items 1 and 2 of Table 6.2. The hazard ratio for DFS was extracted directly from a trial comparing TAC to FAC.[47] This was applied to the baseline hazard of recurrence in the manufacturer's model to calculate DFS on the TAC regimen. The baseline hazard in the manufacturer's submission represents 4 cycles AC, which may be viewed as inferior to 6 cycles FAC. If this is the case, we would expect TAC to appear more effective relative to AC, and so this indicative analysis is expected to underestimate DFS on TAC and hence provide a conservative estimate of the relative cost-effectiveness of TAC.

The changes that have been made to the AC-D3 arm in creating a TAC arm are detailed in Table 6.5. Adverse event rates from the AC-D3 arm were used as an approximation for adverse events in the TAC regimen. This is recognised as a limitation of the analysis. Although a TAC regimen has 6 cycles of docetaxel compared to 4 cycles in the AC-D3 arm, overall chemotherapy is given for 2 more cycles in the AC-D3 arm, and the dose of docetaxel is higher.

Table 6.5. Details of assumptions made by the ERG in creating a licensed docetaxel comparator for the model

	Elements	*Assumption Made*	*Justification/Limitations*
1.	Hazard Ratio	The hazard ratio for the risk of relapse (0.72) was taken from the BCIRG 001 trial[47]	The BCIRG 001 trial[47] compares TAC with 6 cycles of FAC, a regimen which is widely recognised by the clinical community to be more effective than 4 cycles of AC. Therefore, this hazard ratio for TAC is a 'worst case scenario' on the true hazard ratio of TAC against AC, since TAC is being compared against a more effective comparator.
2.	Costs	a. Drug costs were taken from the BNF 50, and calculated for 75mg/m^2 docetaxel, 50mg/m^2 doxorubicin, and 500mg/m^2 cyclophosphamide as per the BCIRG 001 trial.[47] b. 2 hours of administration per cycle were assumed, as the docetaxel part of the dose is administered prior to the doxorubicin / cyclophosphamide part of the dose.	These costs reflect the appropriate costs for treatment costs for TAC if the manufacturer's approach to costing administration is accepted. The cost of pre-medication is omitted in line with the manufacturer's calculation of paclitaxel costs. This would bias the results in favour of AC-P3.

Results from this indicative analysis are shown in Table 6.6.

Table 6.6. Stochastic results of the analysis including an indicative licensed docetaxel comparator

Treatment Arm	Cost	QALY	ICER	Probability cost effective for maximum WTP:		
				£10,000	£20,000	£30,000
AC	£11,169	9.39		0.02	0.00	0.00
AC-P3	£15,648	10.16	5848	0.35	0.23	0.18
TAC	£19,675	10.80	6246	0.63	0.77	0.82

The indicative analysis shows the licensed docetaxel arm to have an ICER of £6,246 compared to the AC-P3 treatment regimen. At a cost-effectiveness threshold of £30,000 per QALY, the model indicates an 82% chance of TAC being cost-effective. However, it must again be stressed that this is only an indicative analysis using the manufacturer's model, and that a more systematic and comprehensive approach to the economic analysis may give different results.

Chapter 7
Discussion and conclusions

7.1 Summary of clinical effectiveness issues

The major flaw in the submission was the absence of a systematic literature review. The manufacturer limited the clinical evidence to 3 trials without providing any justification for their selection, however these were all relevant trials to have included. Additional work by the ERG identified at least one additional trial that should have been included in the submission. Whilst the trial evidence around paclitaxel appears to show modest benefit, the trials themselves may not be directly applicable to the clinical situation that these patients are likely to face.

A further shortcoming of the submission was in not clearly defining the choice of comparator(s). Discussions with oncology experts suggest that whilst the main comparator included by the manufacturer, 4 cycles of AC, was an appropriate standard of care previously, it may not currently be considered the optimal chemotherapy regimen in this higher risk group of patients. This view is supported by Adjuvant! Online. If 4 cycles of AC is now considered to be inferior to current, more modern, modalities of treatment it could be argued that there is a need for further research to assess the benefit of taxanes in conjunction with these new regimens, before making any recommendation for use outwith clinical trials. Within the context of this review, it is not possible for the ERG to comment on the relative clinical effectiveness of paclitaxel as compared to more appropriate, and potentially more effective, comparators.

7.2 Summary of cost-effectiveness issues

The manufacturer did not undertake a systematic review for previously published evidence on the cost-effectiveness of paclitaxel. Instead they submitted a *de novo* economic evaluation which made use of a Markov state-transition model. A number of issues compromise the validity of the model results:

i) the failure to conduct a systematic review for any model parameters, in particular;
ii) the inclusion of a weak comparator to represent standard therapy in the UK NHS;
iii) the failure to explore sub-groups within the overall patient population;
iv) and a number of technical errors in executing the model.

Whilst the economic model may have indicated that the addition of 4 cycles of paclitaxel to 4 cycles of AC may be cost-effective compared to providing 4 cycles AC only, this comparison

is not informative to current clinical practice in the UK NHS. In the context of this review, it is not possible for the ERG to predict the cost-effectiveness of paclitaxel as compared to more appropriate, and potentially more effective, relevant comparators such as 6 cycles of FAC or the licensed indication of docetaxel.

7.3 Implications for research

The manufacturer's submission highlighted that there are a large number of potentially relevant trials still ongoing, many of which will report in the next 6-12 months (www.cancer.gov/search/clinical_trials). Future work is necessary in order to make a comparison between all relevant treatment strategies for women diagnosed with early-stage, operable, node-positive breast cancer and to determine the potential place of paclitaxel within clinical practice in the UK NHS. A full systematic review and meta-analysis of trials assessing taxanes (paclitaxel and docetaxel), and other relevant adjuvant chemotherapy regimens that do not contain taxanes, could inform such a comparison.

References

1. Bristol-Myers Squibb Pharmaceuticals Ltd. Taxol® (paclitaxel) for the adjuvant treatment of early breast cancer, 2006.
2. BMS. Taxol Summary of Product Characteristics: Electronic Medicines Compendium, 2005.
3. Henderson IC, Berry DA, Demetri GD, Cirrincione CT, Goldstein LJ, Martino S, et al. Improved outcomes from adding sequential Paclitaxel but not from escalating Doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. *J Clin Oncol* 2003;21(6):976-83.
4. Mamounas EP, Bryant J, Lembersky B, Fehrenbacher L, Sedlacek SM, Fisher B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. *J Clin Oncol* 2005;23(16):3686-96.
5. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer: results of North American Breast Cancer Intergroup Trial E1199. San Antonio Breast Cancer Symposium; 2005; San Antonio.
6. NICE. Specification for manufacturer/sponsor submission for Single Technology Appraisal (STA) (draft for consultation): National Institute for Health and Clinical Excellence, 2006.
7. Office for National Statistics. Health - Breast Cancer: National Statistics and ONS, 2006.
8. Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence 2003 Report. 2003.
9. Welsh Cancer Intelligence and Surveillance Unit. Incidence of male breast cancer in Wales, 2003 - Personal Communication 2003.
10. Office for National Statistics. Registrations of cancer diagnosed in 2003, England. In: Statistics N, editor, 2003:34 and 48.
11. Office for National Statistics. Cancer Survival: England and Wales, 1991-2001, four major cancers. 2001.
12. Sainsbury JRC, Anderson TJ, Morgan DAL. ABC of breast disease: Breast cancer. *British Medical Journal* 2000;321:745-50.
13. Bundred NJ, Morgan DAL, Dixon JM. ABC of Breast Diseases: Management of regional nodes in breast cancer. *British Medical Journal* 1994;309:1222-5.
14. Sant M, Allemani C, Capocaccia R, et al. Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. *International Journal of Cancer* 2003;106:416-22.
15. Fisher CJ, Egan MK, Smith P, al. e. Histopathology of breast cancer in relation to age. *British Journal of Cancer* 1997;75(4):593-6.

16. ABPI. Target Breast Cancer, 2005:9-12.
17. National Institute of Clinical Excellence. Guidance on Cancer Services - Improving Outcomes in Breast Cancer - Manual Update. 2002.
18. Olivotto IA, Bajdik CD, Ravdin PM, Speers CH, Coldman AJ, Norris BD, et al. Population-based validation of the prognostic model ADJUVANT! for early breast cancer. *Journal of Clinical Oncology* 2005;23(12):2716-2725.
19. Peele PB, Siminoff LA, Xu Y, Ravdin PM. Decreased use of Adjuvant Breast Cancer therapy in a Randomized Controlled Trial of a Decision Aid with Individualized Risk Information. *Medical Decision Making* 2005;25(3):301-307.
20. Adjuvant! Adjuvant Online Website, 2006.
21. Joint Formulary Committee. *BNF 50*. London: BMJ Publishing Group Ltd and Royal Pharmaceutical Society of Great Britain, 2006.
22. Sanofi-Aventis. Taxotere Summary of Product Characteristics: Electronic Medicines Compendium, 2005.
23. Early Breast Cancer Trialists' Collaborative Group. Multi-agent chemotherapy for early breast cancer. *The Cochrane Database of Systematic Reviews* 2001(4).
24. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365:1687-1717.
25. Verrill M. Telephone conversation with Dr Mark Verrill 10th Feb. In: Group ER, editor, 2006.
26. Buzdar AU, Singletary SE, Valero V, Booser DJ, Ibrahim NK, Rahman Z, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomized trial. *Clin Cancer Res* 2002;8(5):1073-9.
27. Citron ML, Berry DA, Cirrincione C, Hudis C, Winer EP, Gradishar WJ, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003;21(8):1431-9.
28. Bloomfield D. Telephone conversation with Dr David Bloomfield 20th Jan, 2006.
29. Ring AE, Ellis PA. Taxanes in the treatment of early breast cancer. *Cancer Treat Rev* 2005;31(8):618-27.
30. Sanofi-Aventis. Taxotere - Incidence of neutropenia. In: Macfarlane K, editor, 2006:Letter re incidence of neutropenia following telephone call to Sanofi-Aventis Medicines Information dept.

31. Buzdar AU. Personal email communication. In: Macfarlane K, editor, 2006:Email conversation on 1st Feb 2006.
32. National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology V2. 2006.
33. National Institutes of Health. Adjuvant therapy for breast cancer- Consensus Development Conference Statement. 2000.
34. Goldhirsch A, Glick JH, Gelber RD, al e. St Gallen International Consensus Guidelines. Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer 2005.

. *Annals of Oncology* 2005;16:1569-83.
35. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer. *NEJM* 2005;353(16):1673-84.
36. NICE. Guide to the Methods of Technology Appraisal. London: National Institute for Health and Clinical Excellence, 2004.
37. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the Economic Evaluation of Health Care Programmes: Third Edition*. Oxford: Oxford University Press, 2005.
38. Bonadonna G, Valagussa P, Moliterni A, Zambetti M, Brambilla C. Adjuvant Cyclophosphamide, Methotrexate, and Fluorouracil in Node-Positive Breast Cancer: The Results of 20 Years Follow-Ip. *New England Journal of Medicine* 1995;332:901-906.
39. Johnston K. Modelling the future costs of breast screening. *European Journal of Cancer* 2001;37:1752-1758.
40. Patient-rated utilities in postmenopausal early breast cancer (EBC): a cross-country comparison. ISPOR Seventh Annual European Congress; 2004; Hamburg, Germany.
41. Hillner BE, Smith TJ. Efficacy and cost effectiveness of adjuvant chemotherapy in women with node negative breast cancer. *New England Journal of Medicine* 1991;324:160-168.
42. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. *Journal of Clinical Epidemiology* 1997;50(6):683-691.
43. Briggs AH, Ades AE, Price MJ. Probabilistic Sensitivity Analysis for Decision Trees with Multiple Branches: Use of the Dirichlet Distribution in a Bayesian Framework. *Medical Decision Making* 2003;23(4):341-350.
44. Hennekens CH, Buring JE. Evaluating the role of chance. In: Mayrent SL, editor. *Epidemiology in medicine*. Philadelphia: Lippincott Williams & Wilkins, 1987.

45. Brown RE, Hutton J, Burrell A. Cost-effectiveness of treatment options in advanced breast cancer in the UK. *PharmacoEconomics* 2001;19(11):1091-1102.
46. Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. *Centre for Health Economics Discussion Paper* 1999;172.
47. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, Weaver C, et al. Adjuvant docetaxel for node-positive breast cancer. *New England Journal of Medicine* 2005;352(22):2302-2313.
48. Stanley A. Abridged version of the American Joint Committee on Cancer Collaborative Staging Manual – Breast Cancer. . *Hospital Pharmacist* 2004;11:409-11.
49. ASCO. American Society of Clinical Oncology, People Living With Cancer website, 2002.
50. Nowak AK, Wilcken NR, Stockler MR, Hamilton A, Ghersi D. Systematic review of taxane-containing versus non-taxane-containing regimens for adjuvant and neoadjuvant treatment of early breast cancer. *Lancet Oncol* 2004;5(6):372-80.
51. Trudeau M, Charbonneau F, Gelmon K, Laing K, Latreille J, Mackey J, et al. Selection of adjuvant chemotherapy for treatment of node-positive breast cancer. *Lancet Oncol* 2005;6(11):886-98.
52. Campone M, Fumoleau P, Bourbouloux E, Kerbrat P, Roche H. Taxanes in adjuvant breast cancer setting: which standard in Europe? *Crit Rev Oncol Hematol* 2005;55(3):167-75.
53. Piccart MJ, de Valeriola D, Dal Lago L, de Azambuja E, Demonty G, Lebrun F, et al. Adjuvant chemotherapy in 2005: standards and beyond. *Breast* 2005;14(6):439-45.
54. Smith I, Chua S. Medical treatment of early breast cancer. III: chemotherapy. *BMJ* 2006;332(7534):161-2.

Appendix 1.[48] Abridged version of the American Joint Committee on Cancer Collaborative Staging Manual – Breast Cancer.

T0	No palpable tumour
T1	Tumour <2cm with no fixation to underlying muscle
T2	Tumour >2cm but <5cm with no fixation
T3	Tumour maximum diameter >5cm
T4	Tumour of any size with fixation to the chest wall or ulceration of the skin
N0	No palpable axillary lymph nodes
N1a	Palpable nodes not thought to contain tumour
N1b	Palpable nodes though to contain tumour
N2	Nodes >2cm or fixed to one another and deep structures
N3	Supraclavicular or infraclaivcular nodes
M0	No clinically apparent distant metastases
M1	Distant metastases are present

“a” indicates no attachment to the underlying muscles; “b” indicates there is attachment; T=tumour; N=node; M=metastases.

Correlation of UICC and TNM classifications of tumours

UICC Stage	TNM Classification
I	T1, N0, M0
II	T1, N1, M0; T2, N0-1, M0
III	any T, N2-3, M0; T3, any N, M0; T4, any N, M0
V	any T, any N, M1

Appendix 2.[49] Breast Cancer Stage Grouping

Source: American Society of Clinical Oncology. www.asco.org. The original source for this material is the American Joint Committee on Cancer (AJCC) Cancer Staging Manual Sixth Edition (2002).

Stage 0: Ductal carcinoma in situ is cancer that has not spread past the ducts or lobules of the breast (the natural boundaries). It is also called non-invasive cancer.

Stage I: The tumour is small and has not spread to the lymph nodes.

Stage IIa: Any one of these conditions:

- The tumour is smaller than or equal to 2 cm, and has spread to the axillary lymph nodes under the arm.
- The tumour is between 2 cm and 5 cm, but has not spread to the axillary lymph nodes.
- There is no evidence of a tumour in the breast, but there is cancer in the axillary lymph nodes.

Stage IIb: Any one of these conditions:

- The tumour is between 2 cm and 5 cm, and has spread to the axillary lymph nodes.
- The tumour is larger than 5 cm, but has not spread to the axillary lymph nodes.

Stage IIIa: Any of these conditions:

- The tumour is smaller than 5 cm, and has spread to the axillary lymph nodes
- The tumour is larger than 5 cm, and has spread to the axillary lymph nodes.

Stage IIIb: The tumour has spread to the chest wall or caused swelling or ulceration of the breast or is diagnosed as inflammatory breast cancer. It may or may not have spread to the lymph nodes under the arm, but has not spread to other parts of the body.

Stage IIIc: Tumour of any size that has not spread to distant parts of the body, but has spread to the lymph nodes in the N3 group.

Stage IV: The tumour can be any size and has spread to distant sites in the body, usually the bones, lungs, liver, or chest wall.

Appendix 3. Search strategy undertaken by ERG for paclitaxel STA

Clinical effectiveness literature review

Inclusion criteria:

Participants: Female; operable node-positive early breast cancer.

Interventions: Paclitaxel, alone or in combination with anthracycline, administered adjuvant to surgical resection. Endocrine if consistent between groups.

Comparator: Chemotherapy regimens NOT including paclitaxel

* Restricted inclusion to only those comparing like with like. E.g. X vs. X+P, or XXX vs. XXX+P.

Outcomes: Disease-free-survival (DFS); overall survival (OS); recurrence, adverse events.

Exclusion criteria:

Participants: Male; advanced stage disease; neo-adjuvant chemotherapy.

Interventions: Paclitaxel administered in the adjuvant setting where the comparator is NOT the same underlying regimen as in the paclitaxel arm. * See notes above

Study selection: Peer review panel

DRUG NAME: **PACLITAXEL**

SYNONYM(S): NSC-125973

COMMON TRADE NAME(S): Taxol®, Anzatax®

Databases searched :-

Database: MEDLINE,

Host: OVID

Date search run: January 11 2006

Date span of search: 1966 to January Week 1 2006

Database: EMBASE

Host: OVID

Date search run: January 12 2006

Date span of search: 1980 to 2006 Week 1

Search strategy: as Medline

Database: CINAHL

Host: OVID

Date search run: January 12 2006

Date span of search: 1982 to December Week 2 2005

Search strategy: as Medline

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Host: OVID

Date search run: January 13 2006

Date span of search: 1st Quarter 2006

Search strategy: as Medline

Search strategy:

#1 taxol.tw.
#2 anzatax.tw.
#3 paclitaxel.mp. or exp PACLITAXEL/
#4 Taxoids/
#5 taxanes$.tw.
#6 or/1-5
#7 [exp *Breast Neoplasms/]
#8 ((breast$ or mamma$) adj5 (cancer$ or carcin$ or tumor$ or tumours or neoplasm$)).tw.
#9 7 or 8
#10 limit 9 to clinical trial
#11 limit 3 to (humans and yr="1986 - 2006")
#12 randomised controlled trial.pt.
#13 controlled clinical trial.pt.
#14 Randomised Controlled Trials/
#15 random allocation/
#16 double blind method/
#17 Single-Blind Method/
#18 12 or 13 or 14 or 15 or 16 or 17
#19 clinical trial.pt.
#20 [exp clinical trials/]
#21 PLACEBOS/
#22 placebo$.ti,ab.
#23 random$.ti,ab.
#24 research design/
#25 (clin$ adj25 trial$).ti,ab.
#26 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

#27 or/19-26
#28 (animals not human).sh.
#29 18 not 28
#30 27 not 28
#31 30 or 29
#32 Comparative Study/
#33 [exp Evaluation Studies/]
#34 Follow-Up Studies/
#35 Prospective Studies/
#36 (control$ or prospectiv$ or volunteer$).ti,ab.
#37 or/32-36
#38 37 not 28
#39 38 not (29 or 31)
#40 34 or 31 or 39
#41 9 and 40
Individual comparators added to search strategy.

FAC
FEC
AC
EC
Docetaxel

* Relevant comparators not clearly defined – used above –with paclitaxel MESH heading should have covered all bases.

Relevant systematic reviews were hand-searched in order to identify any further clinical trials.

RELEVANT TRIALS IDENTIFIED FOR INCLUSION

Relevant clinical trials

3-5 26 27

RELEVANT ONGOING STUDIES

The following databases were searched for current research: Current Controlled Trials register (searched across multiple registers, including, ISRCTN, MRC NHS, and the National Institutes of Health registers), proceedings of the American Society for Clinical Oncology, National Research Register and the National Cancer Institute.

All relevant trials were included in the manufacturer's submission. No additional relevant trials (due to report within 6-12 months) were identified in the search.

* Some of the trials included in the submission are unlikely to report within the next 6-12 months. However, it is often very difficult to predict the timing of results as this is seldom reported in the registry. Generally assumptions are made based upon the starting date of the trails and any information regarding recruitment accrual/status.

Appendix 4. Structured critical appraisal of trial CALGB 9344

PACLITAXEL

NICE STA - CRITICAL APPRAISAL

Name of Trial: Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer

Reference: Henderson I C, Berry D A, Demetri G D *et al.* J Clin Oncol 2003;21: 976-83

Question: : Firstly is there any advantage to increasing the dose of doxorubicin in a commonly used chemotherapy regimen for patients with recently diagnosed breast cancer and histologically involved lymph nodes and secondly is there any advantage for adding paclitaxel to this regimen administered at any doxorubicin dose level?

Did the study ask a clearly focussed question?

Yes - The study was designed to address two main questions: Is there any advantage to increasing the dose of doxorubicin in a commonly used chemotherapy regimen for patients with operable breast cancer and histologically involved lymph nodes? Is there any advantage for adding paclitaxel to this regimen administered at any doxorubicin dose level?

Eligible patients had operable breast cancer with clear surgical margins and metastases to axillary nodes. Systemic therapy started within 84 days of the patient's last surgery.

3121 women were randomised to one of three doses of doxorubicin (60, 75 or 90 mg/m^2) plus cyclophosphamide (600 mg/m^2) for four cycles (CA). A second randomisation allocated women to a further four cycles of paclitaxel (175 mg/m^2) (T) or no additional chemotherapy. Filgrastim (granulocyte colony-stimulating factor (G-CSF), 5µg/kg/d and ciprofloxacin, 750 mg twice daily were given routinely to patients receiving 90 mg/m^2 of doxorubicin, but only after an episode of febrile neutropenia for other patients. Most patients (94%) whose tumor expressed either an oestrogen receptor or progesterone receptor received tamoxifen with a recommended duration of 5 years; 21% of receptor negative patients also received tamoxifen.

The primary end point was duration of disease free survival. Overall survival and toxicity assessment were secondary end points.

Was the study design appropriate?
Yes - To answer two questions in one study it was a 3 x 2 factorial design. Neither doxorubicin dose escalation nor the use of taxane had previously been evaluated in the adjuvant setting.

Three doxorubicin doses were used to allow for estimating the slope of the dose-response curve and to identify any dose that might skew an estimate of dose effect because it is on a threshold or at a plateau of the dose response curve.

After completion of chemotherapy, radiation therapy was administered if the patient was treated with lumpectomy or at the discretion of the physician if the patient was treated with a mastectomy, and tamoxifen was administered for five years if the tumour was receptor positive

Were participants appropriately allocated to intervention and control groups?
Yes - Patients were randomly assigned with equal probability to one of six treatment combinations using a stratified random permuted block design. The number of positive axillary nodes was used as the only stratification factor. (1-3, 4-9, ≥10 positive nodes). The study was not powered to evaluate the effects in subsets.
There were no significant imbalances in the randomisation. No adjustments in p values have been made for multiple comparisons.

Were participants, staff and study personnel 'blind' to participants study group?
No - No attempt was made to blind observers.

Were all of the participants who entered into the trial accounted for at its conclusion?
Can't tell - The published study states that 3,170 patients were randomly assigned and began treatment, 3121 were available for analysis. 49 patients never received any protocol therapy and no information is available on their survival.

Were the participants in all groups followed up and data collected in the same way?
Yes - All patients were evaluated every three months during year 1, twice annually for the next 2 years, and annually thereafter. Left ventricular ejection fraction was measured at baseline and again at five years. A mammogram and chest x-ray were obtained at entry and

then yearly. A bone scan was required before treatment was started, but this requirement was discontinued, consistent with changes in clinical practice, after 2,178 patients had been enrolled. Complete blood counts were obtained twice weekly. All toxicities of grade 2 or greater were collected on the first 325 patients enrolled onto the trial. Only toxicities of grades 3 or higher were routinely recorded on patients after the Data and Safety Monitoring Board had reviewed toxicity data from the first 325 patients.

Was the study large enough?

Yes - The planned sample size of 3000 patients provided 95% power to test for the main effects (dose of doxorubicin and addition of paclitaxel) and greater than 80% power to test for the presence of interaction in the 3 x 2 factorial design.

How are the results presented and what is the main result?

At five years the disease free and overall survival were superior for patients receiving paclitaxel in addition to AC (70% vs 65%, p=0.0023, and 80% vs 77%, p=0.0064)

At 5 years, the disease free survival was 69%, 66% and 67% for patients randomly assigned to 60, 75 and 90 mg/m^2 doxorubicin. Overall survival for these three treatment groups at the same point was 79%, 79% and 77% respectively. There was no interaction between doxorubicin dose and the addition of paclitaxel. Each paclitaxel arm performed better than the corresponding CA arm without paclitaxel.

Although the subsets were not powered to show a difference, the effect of adding paclitaxel to CA proved particularly advantageous among two subsets;
those tumours that were oestrogen receptor negative/unknown (hazard ratio for recurrence 0.72, 95% CI 0.59-0.86), compared with those that were positive (hazard ratio for recurrence 0.91, 95% CI 0.78-1.07) and patients who did not receive tamoxifen (hazard ratio 0.69, 95% CI 0.57-0.84) compared to those that did (hazard ratio 0.92, 95% CI 0.79-1.08). However, the differences between the effects in these subsets were no longer significant after adjusting for multiple comparisons.

How precise are the results?

Adding paclitaxel to the CA combination led to a decrease in the hazard of recurrence of 17% (hazard ratio =0.83) for recurrence and 18% (hazard ratio of 0.82) for death. The 95% confidence intervals are narrow and do not cross the line of no effect for recurrence or death respectively (0.73 to 0.94 and 0.71 to 0.95).

The absolute difference in 1 year disease fee survival and overall survival between the CA and CA plus paclitaxel arms was 3% and 1% respectively. An improvement of 5% in disease-free and 3% in overall survival is now evident at 5 years.

How safe were the regimens?

Most patients (98%) who began CA treatment completed all four cycles of therapy, but dose reductions and delays in the initiation of a treatment cycle were significantly more frequent at the higher doxorubicin doses ($p<0.0001$) Severe neutropenia, thrombocytopenia, anaemia, blood or platelet transfusions and hospitalisations increased in frequency with each doxorubicin dose increase ($p<0.0001$, linear trend in doxorubicin dose).

58 patients randomly assigned to receive paclitaxel did not receive any; the most common reason was withdrawal of consent (41 out of 58 patients). 92% of the patients who started paclitaxel completed all four cycles.

Can the results be applied to the local population?

The study was conducted in North America, no patients were from the UK. However there are unlikely to be significant differences that would affect the suitability of extrapolating the trial outcomes to the UK.

The licensed dose of paclitaxel was used in the trial (175 mg/m^2) and was given as three hourly infusions every three weeks for four cycles.

In the study 60% patients were under 49 years old. The risk of breast cancer rises slowly until the perimenopausal years, levelling off at about the age of 75. It is unclear whether the study represented a typical age range.

54% patients had four or more involved axillary lymph nodes. It would be interesting to determine whether this is average.

In the study 66% of patients had hormone receptor positive tumours. It is believed that between two thirds and three quarters of all breast tumours are stimulated by oestrogen. This is slightly higher than the study population.

Summary

The addition of four cycles of paclitaxel after the completion of a standard course of CA improved slightly the disease-free and overall survival of patients with early breast cancer.

Appendix 5. Structured critical appraisal of trial NSABP B-28

PACLITAXEL

NICE STA - CRITICAL APPRAISAL

Name of Trial: Paclitaxel after Doxorubicin Plus Cyclophosphamide as Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results from NSABP B-28.[1]

Reference: Mamounas E P, Bryant J B, Lembersky B *et al.*J Clin Oncol 2005,23:3686-96

Question: To determine whether four cycles of adjuvant paclitaxel (PTX) after four cycles of adjuvant doxorubicin/cyclophosphamide (AC) will prolong disease free survival (DFS) and overall survival (OS) compared with four cycles of AC alone, in patients with resected operable breast cancer and positive axillary nodes.

Did the study ask a clearly focussed question?

Yes – This study was designed to determine whether four cycles of adjuvant paclitaxel (PTX) after four cycles of adjuvant doxorubicin/cyclophosphamide (AC) would prolong disease free survival (DFS) and overall survival (OS) compared with four cycles of AC alone, in patients with resected operable breast cancer (BC) and histologically positive axillary nodes. 3,060 patients were randomly assigned (AC, 1,529; AC→PTX, 1,531). Patients ≥ 50 years and those younger than 50 years with oestrogen receptor or progesterone receptor positive tumours additionally received tamoxifen for 5 years, starting with the first dose of AC. Patients treated with lumpectomy received whole breast irradiation, following the last cycle of chemotherapy and after recovery from any toxicity. Median follow up was 64.6 months (5.4 years). AC patients received doxorubicin 60mg/m^2 followed by cyclophosphamide 600mg/m^2 every 21 days for four cycles. AC→PTX patients received the same regimen followed by four additional 21-day cycles of paclitaxel 225mg/m^2 as a 3-hour infusion on day 1 of each cycle. The primary end points were disease free survival (DFS) and overall survival (OS).

Was the study design appropriate?

Yes – This study was a randomised, controlled trial. Eligible patients had resected, operable adenocarcinoma confined to the breast and ipsilateral axilla on clinical examination, and were randomly assigned within 63 days from initial cytologic or histologic diagnosis. Patients had to have undergone either lumpectomy plus axillary node dissection or modified radical

mastectomy, and the tumour had to be invasive adenocarcinoma with at least one positive axillary lymph node on examination. Determination of oestrogen (ER) and progesterone (PR) receptor status was performed before assignment. Patients also needed to have normal haemotologic, hepatic and renal parameters and a life expectancy of at least 10 years (excluding diagnosis of cancer). Patients with a previous history of invasive BC or ductal carcinoma in-situ (in either breast) were ineligible, as were patients who had received any prior radiation, chemotherapy, immunotherapy or hormonal therapy for their present BC. Definitive analysis was scheduled to take place after the report of the 490th death on both treatment arms combined.

Were participants appropriately allocated to intervention and control groups?
Yes – A total of 3,060 were randomly assigned to AC (1,529) and AC→PTX (1,531). Thirteen patients in the AC arm and 11 in the AC→PTX arm were declared ineligible for various reasons, most commonly because the time from biopsy to random assignment was > 63 days (6 and 4 patients respectively) and there was advanced disease at random assignment (2 and 3 patients respectively). Patient assignment was balanced with respect to histologic nodal status, assigned tamoxifen administration, type of surgery and institution using a biased-coin minimization algorithm. Random assignment was performed centrally. The analyses reported are based on the intent to treat principle, and included all patients with follow up, whether eligible or not, and regardless of the treatment actually received. Baseline characteristics (patient and tumour characteristics) were evenly distributed between both arms. 67.2% of patients were aged between 40-59 years.

59.2% had a clinical tumour size ≤ 2.0cm. 69.9% had between 1 – 3 positive nodes, and 4.1% had ≥ 10 positive nodes. 66.0% and 61.3% were oestrogen and progesterone receptor positive, with 84.5% assigned tamoxifen treatment.

Were participants, staff and study personnel 'blind' to participants study group?
No – No mention was made of blinding, but as there was no formal comparator, it is assumed that at least the participant, and possibly direct –line staff, were not blind as to which arm the participant was in. Observer bias would be unlikely in this trial as the endpoints were clearly measurable. Participating sites faxed the required entry materials to the NSABP Biostatistical centre and random assignment was performed centrally. Patients treatment assignments were then faxed back to the sites. Before each cycle of PTX, patients were required to receive pre-medication (dexamethasone 20mg PO, 12 and 6 hours before PTX, diphenhydramine 50mg IV, 1 hour before PTX and cimetidine 300mg IV or

ranitidine 50mg IV 1 hour before PTX) so it would have been virtually impossible to blind the participants and direct-line staff.

Were all of the participants who entered into the trial accounted for at its conclusion?
No – However, only one patient contributed no follow up. Of the 1,529 patients in the AC arm, all but one had positive follow up. Of the 1,531 AC→PTX patients, all had follow up. Vital status after 5 years is known in 78.7% of the AC arm and 79.9% of the AC→PTX arm. More than 98% patients completed all four cycles of AC. 8.8% of the AC→PTX arm did not start PTX (88% due to patient withdrawal as opposed to clinician withdrawal). The chemotherapy completion rate dropped during administration of PTX with 75.9% of patients completing all 8 cycles. For patients in the AC→PTX arm in which PTX treatment began but was discontinued before completion of 8 cycles, physician withdrawal was the reason in 53% cases, patient withdrawal accounted for 47%. No further information was given on these withdrawals. It would have been useful to have known the reasons for these withdrawals. The analyses reported are based on the intent to treat principle, and included all patients with follow up, whether eligible or not, and regardless of the treatment actually received.

Were the participants in all groups followed up and data collected in the same way?
Yes – All patients were followed up in the same way.

History and physical exams took place before treatment. Patients also needed to have history and physical examinations along with haematologic studies and chemistries on day 1 before each cycle of chemotherapy and every 6 months for the first 5 years. Gynaecological examinations (where applicable), chest x-ray and mammograms were required yearly for the first 5 years. Only physical examination, gynaecologic examination (where applicable) and mammogram were required annually after 5 years. The two groups appeared to have been followed up in the same way.

Was the study large enough?
Yes – Initially the sample trial size was 2,450 patients, but after a review of the early data indicated a lower percentage of patients completed all 4 PTX cycles than was originally projected, the target sample size was increased to 3,050 patients. Definitive analysis was scheduled to take place after the report of the 490th death on both treatment arms combined. This ensures a power of 80% to detect a 22.6% reduction in mortality rate, in order to provide for a potentially attenuated treatment effect caused by non-completion of therapy. In order to account for early interim looks, the final analysis is based on a 0.0452 two-sided level of significance. In effect 498 deaths occurred in both treatment arms.

How are the results presented and what is the main result?

DFS – There were 463 DFS events in the AC arm and 400 in the AC→PTX arm. The addition of PTX reduced the risk of a DFS event by an **absolute risk reduction (ARR) of 4.2%** (RR 0.83; 95% CI, 0.72-0.95; p=0.006). The 5-year DFS for AC patients was 72% +/- 2% compared with 76% +/- 2% for those in the AC→PTX arm.

OS – There were 255 deaths in the AC arm and 243 in the AC→PTX arm. The addition of PTX gave an **ARR of 0.8%** (RR 0.93; 95% CI, 0.78-1.12; p=0.46). The 5 year OS was 85% +/- 2% for both arms.

The cumulative incidence of all first events was 28.3% for the AC arm and 24.4% for the AC→PTX arm.

Analysis of the effect of PTX on both DFS and OS according to hormone receptor (HR) status showed no significant interaction between the effect of PTX in HR positive compared with HR negative patients.

In **HR positive** patients specifically, the **ARR in DFS events was 5.1%** (RR 0.77; 95% CI, 0.65-0.92; p=0.004). In **HR negative** patients, the **ARR in DFS events was 2.3%** (RR 0.90; 95% CI, 0.72-1.12; p=0.33).

In **HR positive** patients specifically, the **ARR in deaths was 0.6%** (RR 0.94; 95% CI, 0.74-1.21; p=0.64). In **HR negative** patients, the **ARR in deaths was 1.9%** (RR 0.90; 95% CI, 0.70-1.17; p=0.44).

How precise are the results?

The RR for the primary endpoint of DFS was significant (p=0.006). The 95% confidence interval is narrow and does not cross the line of no effect (0.72-0.95), although the ARR at 4.2% is relatively low. OS was not statistically significant (p=0.46) with confidence intervals crossing the line of no effect (0.78-1.12) and an ARR of 0.82%.

How safe were the regimens?

Toxicity was stated as being 'acceptable' for the adjuvant setting. Seven patients died, where treatment couldn't be excluded as a contributing factor. Five deaths occurred in AC patients only, two in AC→PTX. The most common grade 3 or greater toxicity during PTX therapy included neurosensory toxicity in 15% patients, neuromotor toxicity in 7%, arthralgia and/or myalgia in 12%, day 1 granulocytopenia in 3%, febrile neutropenia in 3% and thromboembolic events in 1%. Severe hypersensitivity reactions occurred in 1% of patients

during PTX administration. Incidence of grade 3 or higher cardiac dysfunction was 1% in the AC arm and 0.9% in the AC→PTX arm. There were eight cases of acute myelogenous leukaemia or myelodysplastic syndrome (AML/MDS). Six of these occurred in the AC→PTX arm and two in the AC arm.

Can the results be applied to the local population?

The population in this trial tended to be a younger age of patient; 50.6% were aged 49 years or under, a further 30.8% were aged between 50 and 59 years. The dose of paclitaxel used was also higher than the licensed dose – 225mg/m^2. This may have had an effect on outcomes, although as stated before, OS was not significant. Patients in this trial were at a lower risk of relapse than in the CALGB 9344 trial[2]; in this trial, 30% of patients had over 4 positive lymph nodes involved; the previous CALGB 9344 trial had 54% of patients with over 4. There may also be issues with the use of tamoxifen. In this trial it was used concurrently with the AC chemotherapy, and 85% of trial participants received tamoxifen. One view is that administering concurrent tamoxifen with anthracycline based chemotherapy results in impaired DFS compared with delaying tamoxifen until chemotherapy is completed[3]. This concurrent use in this trial could be a key issue.

Summary

This was a well structured, RCT over a relatively long time period (5.4 years), in 3,060 patients. Primary endpoints were DFS and OS, and the endpoint of DFS was met, with an ARR of 4.2% improvement with the PTX arm (RR 0.83; 95% CI, 0.72-0.95; p=0.006). The endpoint of OS was not met, with an ARR of 0.82% (RR 0.93; 95% CI, 0.78-1.12; p=0.46). The trial incorporated patients with a lower risk of relapse than in the other key trial[2] and used a higher, unlicensed dose of PTX. There are outstanding confounding issues about the high and concurrent use of tamoxifen, and this trial does also not show us whether or not, the benefit in the taxane arm was purely due to the increased duration of treatment, as there was no active comparator. This does not give us any information on the use of taxanes in lymph node negative patients, as only lymph node positive patients were involved. This trial did show that the addition of PTX to AC chemotherapy resulted in a significant improvement in DFS at 5 years.

References

1. Mamounas E P, Bryant J B, Lembersky B et al. Paclitaxel after Doxorubicin Plus Cyclophosphamide as Adjuvant Chemotherapy for Node-Positive Breast Cancer: Results from NSABP B-28. J Clin Oncol 2005;23:3686-96

2. Henderson I C, Berry D A, Demetri G D et al. Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer. J Clin Oncol 2003;21:976-83
3. Ring A E, Ellis P A. Taxanes in the treatment of early breast cancer. Cancer Treatment Reviews (2005);31:618-27

Appendix 6. Structured critical appraisal of trial NABCI E1199

PACLITAXEL

NICE STA - CRITICAL APPRAISAL

Name of Trial: Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer; results of North American Breast Cancer Intergroup Trial E1199.

Reference: Sparano JA, Wang M, Martino S, *et al.* Presented at 2005 San Antonio Breast Cancer Symposium.

Question: Are the outcomes after adjuvant chemotherapy comparable among various docetaxel and paclitaxel regimens?

Did the study ask a clearly focussed question?

Yes - This study was designed to compare the effectiveness of adjuvant paclitaxel (P) with docetaxel (D), and the effectiveness of every 3 week with weekly adjuvant taxanes therapy in patients with operable breast cancer.[1,25] Patients are randomised to receive one of four treatment arms:

All patients received doxorubicin (60mg/m^2 IV.) and cyclophosphamide (600mg/m^2 IV.) every 3 weeks for 4 courses (weeks 1-12).
Arm (I): Beginning at week 13, patients receive paclitaxel (175mg/m^2 IV.) over 3 hours every 3 weeks for 4 courses
Arm (II): Beginning at week 13, patients receive paclitaxel (80mg/m^2 IV.) over 1 hour weekly for 12 weeks.
Arm (III): Beginning at week 13, patients receive docetaxel (35mg/m^2 IV.) over 1 hour weekly for 12 weeks.
Arm (IV): Beginning at week 13, patients receive docetaxel (100mg/m^2 IV.) over 1 hour every 3 weeks for 4 courses.

All patients with oestrogen and/or progesterone receptor (ER/PR)-positive disease also received a 5 year or longer course of adjuvant hormonal therapy, consisting either of tamoxifen (20mg daily) ,an aromatse inhibitor (AI; for post menopausal women given at the

discretion of the treating physician), or tamoxifen followed by an AI. The primary analyses compared taxane (P vs. D) and schedule (every 3 weeks vs. weekly). The primary endpoint was disease-free survival (DFS), defined as local, regional, and/or distant relapse, secondary primary breast cancer, or death without recurrence.

Was the study design appropriate?

Probably - The North American Breast Cancer Intergroup E1199 study was a phase III, randomised, multi-centre study. Eligible patients included women with histologically confirmed operable axillary node-positive or high-risk (tumour at least 2 cm) node-negative breast cancer.

After a median follow-up of 46.5 months the Eastern Cooperative Oncology Group (ECOG) Data Monitoring Committee (DMC) advised release of the data at the fourth planned interim analysis. However, no references to the criteria used for early reporting are given. The trial was sponsored by the National Cancer Institute.

Were participants appropriately allocated to intervention and control groups?

Probably - The NCI clinical trials registry states a projected accrual of 5,000 patients for this study.[3] A schematic of the study design has been omitted from the submission and no method for randomisation is stated. However, reference is made to stratification according to hormone receptor, number of involved lymph nodes, tumour size and type of prior surgery. A total of 4,988 patients are included in the primary analysis; 1,261 received a total of 700mg/m^2 paclitaxel (Arm I), 1,239 received a total of 960mg/m^2 paclitaxel (Arm II), 1,243 received a total of 400mg/m^2 docetaxel (Arm III), and 1,245 received a total of 420mg/m^2 docetaxel (Arm IV). The baseline characteristics of the two groups appear well balanced.

Were participants, staff and study personnel 'blind' to participants study group?

No – The trial was an open-label study. Blinding would not have been possible due to the differing dosing schedules.

Were all of the participants who entered into the trial accounted for at its conclusion?

Can't tell - All participants outlined in the patient characteristics table would appear to have been included in the primary and safety analyses. However, no reference is made to the numbers of patients lost to follow-up, those that may have violated study protocol or whether all participants were analysed by the groups to which they were originally allocated. A CONSORT diagram should have been provided to account for all patients up to entry into an intention-to-treat analysis.

Were the participants in all groups followed up and data collected in the same way?

Can't tell – The NCI registry states that patients were to be followed every 3 months for 2 years, every 6 months for 3 years, and then annually thereafter.[3] However, no reference is given in the submission to the nature or exact scheduling of any of the assessments or investigations to be undertaken at follow-up.

Was the study large enough?

Can't tell - The published abstract states that the trial had an 86% power to detect a 17.5% reduction in failure for either primary comparison (taxane or schedule).[1]

The DMC advised early release of the results at the fourth planned interim analysis, after 856 DFS events (82% of total information) had occurred at a median follow-up of 46.5 months.

No indication is made to the number of events required for this analysis, or to the significance levels underlying the power calculations. Furthermore, no justification is given for the size of the difference that the trial is powered to detect, or whether the calculation takes into account anticipated rates of non-compliance and/or loss to follow-up.

How are the results presented and what is the main result?

Analysis was performed after 856 DFS events, Arm I = 195, Arm II = 230, Arm III = 225, and Arm IV = 206. This was at a median follow-up of 46.5 months. The results are presented in tabulated format with hazard ratios (HR) and p values. The statistical methods employed for these analyses are not stated. Confidence intervals are presented for some of the results reported in the conference abstract, but not for those in the STA submission.

For the primary analyses, there was no significant differences in the DFS when comparing taxane treatment arms (HR, 0.985; p=0.83) or dosing schedule, once weekly versus every 3 weeks (HR, 1.043; p=0.54). When comparing the 'standard' reference arm (arm II) to the other arms the HR was 1.20 (95% CI 0.99-1.46; p=0.06) for arm I, HR 1.13 (0.94-1.36; p=0.20) for arm IV, and HR 1.03 (0.85-1.23; p=0.78) for arm III, respectively.

How safe were the regimens?

There was a higher incidence of grade 3 or 4 adverse events in those patients receiving the larger dose of paclitaxel compared to receiving the smaller dose (24% & 6% vs. 24% &.4%, for arm II and I, respectively). The incidence of grade 3 adverse events was lower, and the incidence of grade 4 higher in those receiving the larger dose of docetaxel compared to the smaller dose (21% & 50% vs. 39% & 6%, for arm IV and III, respectively). Overall neutropenia was more common with docetaxel exposure compared to paclitaxel. Other

grade 3 or 4 adverse events occurring in at least 5% of patients were: infection, stomatitis, fatigue and tearing.

How precise are the results?

This was a large phase III randomised trial. Insufficient data is provided to fully assess the design and conduct of the trial. However, the baseline characteristics of all four treatment groups are well balanced. All participants appear to have been accounted for and followed-up regularly, although insufficient data is provided to confirm this. As no references to the criteria used for early reporting are given, the decision of the DMC to release the data after only 82% of the total information had been collated cannot be validated.

The HR for the primary analysis was non-significant when comparing taxane or schedule (p=0.83 and p=0.54, respectively). No confidence intervals are reported for the primary analysis. Overall there is insufficient data presented to fully assess the validity of the results presented.

Can the results be applied to the local population?

The study was conducted in North America with no patients from the UK. However there are unlikely to be significant differences between the two populations that would affect the suitability of extrapolating the trial outcomes to the UK.

The median age of the participants was 51 years old (range 19-81) all had undergone lumpectomy or mastectomy plus axillary node dissection with a minimum of 6 nodes removed and is therefore representative of UK practice.

The dose of paclitaxel used in the 'standard' reference arm was the licensed dose of 175mg/m^2 every 3 weeks for four cycles.[4] However, docetaxel is licensed at a dose of 75mg/m^2 every 3 weeks for 6 cycles whereas in this study patients received either 100mg/m^2 every 3 weeks for 4 weeks or 35 mg/m^2 weekly for 12 weeks.[5]

Summary

Both paclitaxel and docetaxel, on a weekly or every three week schedule following AC, result in similar outcomes in women with node-positive or high-risk node-negative breast cancer. There was no significant difference in the DFS among those patients treated with adjuvant paclitaxel or those receiving docetaxel. In addition, weekly dosing provided no significant benefit over 'standard' dosing every 3 weeks. Interpretation of the results must take into account the early reporting of the trial. However, the results presented are derived from 82% of the planned information; it would appear unlikely that either comparison would become significant after the full data is obtained. More definitive evaluation will require additional follow-up and further events. Docetaxel was associated with a higher risk of grade 3 and 4

toxicity. Overall, neutropenia was more common with docetaxel exposure compared to paclitaxel.

Although this study provides a direct comparison of taxanes in the adjuvant treatment of breast cancer, insufficient data has been presented to fully assess the validity of this study.

References

1. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in patients with axillary node-positive or high-risk node-negative breast cancer; results of North American Breast Cancer Intergroup Trial E1199. Program and abstracts of the 28th Annual San Antonio Breast Cancer Symposium; December 8-11, 2005; San Antonio, Texas. Abstract 48

2. CCO Independent Conference Coverage. 2005 Annual san Antonio Breast Cancer Symposium. Outcomes after adjuvant chemotherapy comparable among various docetaxel and paclitaxel regimens. Clinical Care Options. http://www.clinicaloptions.com

3. Phase III Randomized Study of Doxorubicin and Cyclophosphamide Followed By Paclitaxel or Docetaxel in Women With Node-Positive or High-Risk Node-Negative Stage II or IIIA Breast Cancer. National cancer Institute Clinical Trials Registry. http://www.nci.nih.gov

4. Taxol® summary of product characteristics, Bristol-Myers Squibb Pharmaceuticals Ltd. at www.medicines.org.uk Accessed on 05.01.2006.

5. Taxotere® summary of product characteristics, Sanofi-aventis. at www.medicines.org.uk Accessed on 05.01.2006.

Appendix 7. Structured critical appraisal of Buzdar *et al.*

PACLITAXEL

NICE STA - CRITICAL APPRAISAL

Name of Trial: Evaluation of Paclitaxel in Adjuvant Chemotherapy for Patients with Operable Breast Cancer: Preliminary Data of a Prospective Randomised Trial.[1]

Reference: Buzdar A U, Singletary S E, Valero V et al. Clin Can Res. May 2002;Vol 8:1073-79.

Question: Paclitaxel was evaluated in an adjuvant setting to determine its impact on reducing the risk of recurrence in patients with operable breast cancer.

Did the study ask a clearly focussed question?

Yes – This study was designed to administer the same number of chemotherapy cycles to all patients, with the difference between the two arms of the study being the substitution of paclitaxel (PTX) in the initial four cycles of chemotherapy. Patients who had intact primary tumours had an initial four cycles of systemic therapy with either PTX 250mg/m^2 every 3 weeks, or 5 fluorouracil (500mg/m^2), adriamycin (doxorubicin 50mg/m^2) and cyclophosphamide (500mg/m^2) (FAC) before local therapy and then received the remaining four cycles of FAC after surgery (the neoadjuvant group). Patients who had received local therapy at time of study entry received all eight cycles of assigned treatment adjuvantly. Patients who were ≥ 50 years of age and whose tumours were oestrogen receptor (ER) positive were subsequently treated with tamoxifen for 5 years. Patients who had undergone breast preservation surgery, or were candidates for radiation therapy for other indications, received irradiation after completion of all chemotherapy.

The primary endpoint was not clearly defined in this paper but was interpreted as being DFS – the objective was to detect an absolute improvement of 15% in a 5-year response to the combination therapy.

Was the study design appropriate?

Yes – This study was a prospective, randomised controlled trial. All patients with histologically confirmed (T_{1-3}, N_{0-1} and M_0) invasive carcinoma of the breast were eligible for the study regardless of whether they had received local therapy for their cancer. Patients were randomised to receive treatment with either eight cycles of FAC or four cycles of paclitaxel followed by four cycles of FAC (Pac/FAC). Chemotherapy modification criteria

were used and chemotherapy escalated according to granulocyte counts, platelet counts and organ toxicity. Doses were reduced by 20% if the patient had organ toxicities of grade 3 or higher.

Were participants appropriately allocated to intervention and control groups?
Yes – All patients were prospectively registered for the study, in an online research database and were stratified by age, tumour status and nodal status. 524 patients were enrolled in the study, with 259 (49%) in the FAC alone arm, and 265 (51%) in the Pac/FAC arm. 56 and 57% respectively were <50 years old, and overall, 77% were white. 34% of FAC patients and 33% of Pac/FAC patients had the treatment neoadjuvantly. There were some differences in ER status; the FAC arm had a lower % of ER +ve patients (55%) compared to the Pac/FAC arm (62%). The two arms differed with respect to pre-surgery clinical stage and post-surgery surgical stage; for both, Pac/FAC had a higher proportion of patients with stage 1 disease. A larger % of patients in the Pac/FAC arm received 8 cycles compared to FAC (88% vs 71%).

Were participants, staff and study personnel 'blind' to participants study group?
No – No mention was made of blinding, it is assumed that at least the participant, and the direct – line staff, were not blind as to which arm the participant was in. Before each cycle of PTX, patients were required to receive pre-medication (dexamethasone 20mg PO, 12 and 6 hours before PTX, diphenhydramine 50mg IV, 1 hour before PTX and cimetidine 300mg IV or ranitidine 50mg IV 1 hour before PTX) so it would have
been virtually impossible to blind the participants and direct-line staff/observer bias would be unlikely in this trial as the endpoints were clearly measurable.

Were all of the participants who entered into the trial accounted for at its conclusion?
No – The results are still interim so no information is provided on unaccountable patients. Incomplete information was available in 17 patients for certain aspects of the baseline characteristics (No. of cycles received (4), irradiation status (11) and tamoxifen treatment (2).

Were the participants in all groups followed up and data collected in the same way?
Yes – A complete history and physical examination were performed on all patients before the start of treatment. Many different checks were repeated at 4-month intervals during the initial 2 year period of the study. They were repeated at 6 month intervals for an additional 1

year, with mammogram and bone scans yearly. After 3 years of follow up, patients were monitored yearly.

Was the study large enough?

Yes – The original protocol specified that analysis would take place after 105 failures, so this data is still considered preliminary, and at the time of this paper, 92 recurrences had occurred. The study was designed to include 518 patients randomised in equal numbers. With this sample size, there would be an 80% power to detect this difference. DFS was estimated by the Kaplan-Meier method.

How are the results presented and what is the main result?

The estimated DFS at 48 months was 0.83 (95% CI, 0.79-0.88) for FAC alone and 0.86 (95% CI, 0.82-0.91) for Pac/FAC. The difference between the two arms was not statistically significant (p=0.09). This equated to an overall estimated reduction in risk (absolute risk reduction ARR) **of 5.8%** in favour of the Pac/FAC arm (HR 0.70; 95%CI, 0.47-1.07, p=0.09).

For ER negative patients, DFS at 48 months was 0.79 for FAC alone and 0.83 for Pac/FAC. **The ARR was 4.5%** (p=0.39).

For ER positive patients, DFS at 48 months was 0.87 for FAC alone and 0.89 for Pac/FAC. **The ARR was 7.4%** (p=0.07).

The trial was initially designed under the assumption that there would be a 60% DFS rate at 5 years in FAC arm, which corresponds to 66% at 4 years. In this study, there is an estimated DFS of 83% at 4 years. Although accrual and follow up were adequate, the results were regarded as preliminary attributable to the lower than expected recurrence rate. At the time of analysis, there had been 47 deaths, 24 in the FAC arm and 23 in the Pac/FAC arm.

How precise are the results?

The RR for the primary endpoint of DFS was not significant (p=0.09). The 95% confidence interval is wide and does cross the line of no effect (0.47-1.07). It must be emphasised that the data is still interim. The results were also underpowered due to lower than anticipated recurrence rates.

How safe were the regimens?

A higher percentage of patients in the Pac/FAC group experienced febrile neutropenia (17%) compared to the FAC group (9%). The same applied to myalgias ≥ grade 3 (12% vs 2%) and paresthesias ≥ grade 3 (6% vs 1%).

Can the results be applied to the local population?

The dose of paclitaxel used was higher than the licensed dose – 250mg/m^2. This may have had an effect on outcomes, although as mentioned before, interim differences were not significant.

Summary

The preliminary results show that differences between FAC for eight cycles and Pac/FAC 4/4 cycles, possibly suggest that the latter regimen can result in a reduction in the risk of recurrence in patients with early breast cancer. However, the differences between the two regimens are not statistically significant, possibly because the time periods are too short and the sample sizes are relatively small. The study was designed to be evaluated after a larger number of recurrences had occurred. The patients in the control arm also had a much lower than expected recurrence rate, which may have affected the results.

To date (January 2005),the final results from this trial have still not been published.

References

1. Buzdar A U, Singletary S E, Valero V et al. Evaluation of Paclitaxel in Adjuvant Chemotherapy for Patients with Operable Breast Cancer: Preliminary Data of a Prospective Randomised Trial. Clin Can Res. May2002;Vol8:1073-79.

Appendix 8. Structured critical appraisal of Citron *et al.*

PACLITAXEL

NICE STA - CRITICAL APPRAISAL

Name of Trial: Randomised Trial of Dose-Dense Versus Conventionally Scheduled and Sequential Versus Concurrent Combination Chemotherapy as Postoperative Adjuvant Treatment of Node-Positive Primary Breast Cancer: First Report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741

Reference: Citron ML, Berry DA, Cirrincione C *et al.* Journal of Clinical Oncology 2003;21:1431-9.

Question: In female patients with axillary node-positive breast cancer, does adjuvant administration of cyclophosphamide, doxorubicin and paclitaxel improve disease-free survival with a dose-dense schedule, or sequential versus concurrent drug administration, and is there an interaction between these factors?

Did the study ask a clearly focussed question?

Yes - The study tested two concepts; the benefits of dose-dense administration and whether there is a difference between sequential and concurrent drug administration.[1] It has been hypothesized that more frequent administration of cytotoxic therapy is more effective than dose escalation at reducing residual tumour burden.[1] Sequential therapy refers to the application of treatments one at a time rather than concurrently.[1]

Patients were assigned to one of four treatment regimens:

1. Doxorubicin 60 mg/m^2 every three weeks for four cycles followed by paclitaxel 175 mg/m^2 every three weeks for four cycles followed by cyclophosphamide 600mg/m^2 every three weeks for four cycles. Total 33 weeks.
2. The same doses and sequence as in 1 but with a treatment interval of two weeks. Total 22 weeks.
3. Doxorubicin 60 mg/m^2 and concurrent cyclophosphamide 600mg/m^2 every three weeks for four cycles, followed by paclitaxel 175 mg/m^2 every three weeks for four cycles. Total 21 weeks.

4. The same doses and sequence as in 3 but with a treatment interval of two weeks. Total 14 weeks.

Additionally, all patients in groups 2 and 4, the dose dense groups, received filgrastim whereas groups 1 and 3 received filgrastim only when medically indicated.

In common with many cancer orientated trials, the primary outcome measure was disease free survival (DFS) and the secondary outcome measure was overall survival (OS).

Was the study design appropriate?
Yes - The study used a 2x2 factorial experimental design to assess the two factors of dose density (2 weeks vs 3 weeks) and treatment sequence (concurrent vs. sequential) and the possible interaction between them.

Were participants appropriately allocated to intervention and control groups?
Yes - The trial was randomised but the method used is not described and although not explicitly stated, there is an indication that the groups were only stratified with respect to the number of positive nodes. The groups appear balanced with respect to many variables and the authors state that the main trial results were unaffected even after adjustment for any group differences.

Were participants, staff and study personnel 'blind' to participants study group?
No. Due to the nature of the treatments in each group, blinding the trial was not practicable.

Were all of the participants who entered into the trial accounted for at its conclusion?
Can't tell - The authors state that 2005 patients were accrued, 32 of whom never received any protocol therapy. The results are therefore based on a total population of 1973. The authors do not state whether the 32 who never received treatment withdrew before randomisation. At the time of writing, the median follow-up was 3 years (range 2 to 5). Follow-up records were good with 99% of all patients with at least 1 year and 92% with at least 2 years. [ref H, pg1434 para 1+4]

Were the participants in all groups followed up and data collected in the same way?

Yes - Aside from the treatment schedule stipulated for each group, all patients were treated identically. Radiotherapy was administered post-chemotherapy and according to local guidelines, and tamoxifen was recommended, but not mandatory, for certain patients. Therefore differences may have existed with respect to these factors.

Was the study large enough?

Can't tell - Using initial assumptions based on a certain rate of patient accrual and using an estimated frequency of events, the trial aimed to recruit a minimum of 1584 patients to provide 90% power to detect a 33% difference in hazard for either main effect. However, due to a greater rate of accrual [ref k, pg1433] than expected, the planned number of patients was increased. The authors do not state whether they were able to maintain this level of statistical power with the numbers actually recruited.

How are the results presented and what is the main result?

The primary and secondary outcomes are comprehensively reported for the main effects with 95% confidence intervals and p values provided. Additionally, the results for the individual treatment groups are similarly reported with respect to the primary outcome.

Graphical representations are provided and appear to be of the Kaplan-Meier survival curve type.

With respect to DFS the effect of drug sequence was not significant, p=0.58. The effect of dose density was significant with the benefit in favour of fortnightly dosing as opposed to three weekly intervals; risk ratio 0.74 (95%CI 0.59-0.93) p=0.010.

With respect to OS the conclusion was the same, with no statistical difference due to drug sequence, p=0.48, but a significant difference with two weekly intervals as opposed to three weekly; risk ratio 0.69 (95%CI 0.50-0.93) p=0.013.

There was no statistically significant evidence of an interaction between these factors (p=0.13).

How safe were the regimens?

Toxicity and safety data are comprehensively reported, as is the incidence of treatment complications. Grade four granulocytopenia was more frequent on the

three-week regimens compared with the dose-dense regimens, 33% vs 6% respectively, p<0.001. Grade ≥3 emesis was significantly more common for the concurrent regimens than for the sequential regimens, 7% vs 3% respectively, p<0.001. It should be remembered that all patients on dose-dense treatment received filgrastim.

How precise are the results?

The precision of the results is good. Most of the confidence intervals, where provided, do not overlap. The upper confidence limit of risk-ratio benefit for dose density with respect to both DFS and OS is 0.93, suggesting that the relative benefit from increasing the dose density may be as little as 7%. This must be balanced against the increased use of filgrastim, which would cost, per patient, approximately £7,455 in regimen 2 or £4,970 in regimen 4 (assuming that patients receive either of the two doses in equal proportions).[2]

Can the results be applied to the local population?

The trial population consisted principally of node-positive early-stage breast cancer patients. The drugs and doses used are licensed in the UK for this indication, although only the regimen 3 administration schedule matches the licensed schedule for paclitaxel.[3] The results provide evidence for the benefit of a dose-dense regimen over the comparator group with the only apparent imposition being the mandatory requirement for filgrastim. Paclitaxel is not licensed in the UK for two-weekly administration. 3 The rationale behind the choice of treatment sequence used in the sequential treatment groups (groups 1 and 2) is not given.

The median length of follow-up for this data is probably insufficient to draw strong enough conclusions to affect practice.

References

1. Citron ML, Berry DA, Cirrincione C et al. Randomised trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of intergroup trial C9741/cancer and leukemia group B trial 9741. Journal of Clinical Oncology 2003;21:1431-9

2. eMIMS, www.emims.net, accessed 01.02.2006.

3. Taxol® summary of product characteristics, Bristol-Myers Squibb Pharmaceuticals Ltd. Accessed at www.medicines.org.uk on 05.01.2006.

Appendix 9 - Systematic Reviews

Six systematic reviews were identified in the literature search performed by the ERG, which have examined clinical trials investigating the use of taxanes in early breast cancer and have provided an overview of the ongoing research in this area. The conclusions of these reviews are discussed below:

Nowak et al. (2004)[50]

Following systematic searching, studies were included if they were randomised, reported in English and included only women with early breast cancer receiving chemotherapy in the neoadjuvant or adjuvant setting, and compared taxane-containing with non-taxane-containing regimens.

Eligibility criteria were applied by two independent reviewers with discrepancies resolved by a third reviewer. Of the twenty five eligible trials identified, ten trials had published data of which five assessed neoadjuvant therapy, four assessed adjuvant therapy and one assessed both adjuvant and neo-adjuvant therapy. All studies had high ratings for trial quality, and their conclusions were judged unlikely to be affected by bias. Taken together, these trials include results from 12 159 evaluable women. The results of this systematic review supported the use of taxanes as adjuvant chemotherapy for women with early breast cancer and involved lymph nodes however no formal meta-analysis was attempted due to limited mature survival data. The strongest support was for the addition of four cycles of paclitaxel to four cycles of doxorubicin and cyclophosphamide, or for the substitution of six cycles of FAC with six cycles of docetaxel, doxorubicin and cyclophosphamide.

This effect was reported as being independent of hormone-receptor status, and the evidence as not supporting restricting the use of taxanes to women with hormone receptor negative tumours. Longer follow-up of all the trials included in this systematic review was suggested to clarify the role of taxanes in the treatment of early breast cancer. Additional trials included in this review are the US Oncology 9735 and BCIRG 001 trials.

Ring and Ellis (2005) [29]

No details of a systematic search are given however seven first generation trials which examine the sequential or concomitant addition of taxanes to adjuvant anthracycline-based chemotherapy and one second generation trial which assumes taxanes are beneficial in the adjuvant setting and examines the different taxanes and dosing regimes are included in this review. No formal meta-analysis is provided. Six of the seven first generation trials included demonstrate an overall survival advantage with the addition of taxanes to anthracycline adjuvant therapy. However limitations with the enrolment of higher risk patients and fewer patients with hormone receptor positive tumours in studies examining sequential addition of taxanes was highlighted. In addition the increases in haematological toxicity seen following combination therapy were noted and the authors concluded that it is by no means certain that combination treatment with an anthracycline and a taxane is an appropriate adjuvant regimen. Critical appraisal of one second generation trial was reported as showing that disease free survival (DFS) and overall survival (OS) are prolonged in dose dense regimens however, the choice of taxane, how best to incorporate it and the optimal doses required have yet to be determined. Additional trials include PACS 01, BCIRG, ECTO and SWOG/ECOG.

Trudeau et al (2005)[51]

Systematic searches using the search terms “adjuvant and breast cancer” or “postoperative and breast cancer” as disease and treatment-specific medical subject headings were performed. Inclusion criteria consisted of studies which reported on the final results of randomised controlled trials, published in English, and investigating the use of adjuvant polychemotherapy in node-positive breast cancer or in node-positive disease and node-negative disease provided the results included a preplanned subgroup analysis on the basis of nodal status. Clinical trials involving standard-dose anthracycline, escalated-dose epirubicin and anthracycline-taxane adjuvant regimens were compared with cyclophosphamide, methotrexate, and fluorouracil regimens to establish which provided the greatest benefit in terms of safety, efficacy, cost and convenience to patients. 16 randomised controlled trials were identified as eligible for review. These studies enrolled more than 15 000 patients with node-positive disease in the adjuvant setting. Two studies were excluded from the analysis as they did not meet minimum numbers of patient’s criteria. Additional trials included in this review are CALGB 8541, NSABP B22, The Belgian Study, The National Cancer Institute of Canada MA5 Study, The French Adjuvant study Group (FASG) 05.

Many studies of escalated-dose epirubicin and anthracycline-taxane regimens were reported as showing survival benefits. It was concluded by the authors that level-one evidence (which would support a change in the standards of clinical practise) had been shown for escalated-dose epirubicin and anthracycline-taxane categories. Based on survival alone the TAC regimen and the FEC100 regimen resulted in the greatest proportional reduction in mortality. When all factors were considered, the TAC regimen, the FEC100 regimen and the CEF regimen were reported to be the best available treatment options.
However the authors commented that the choice of adjuvant chemotherapy should be based on physician training, patient preference and other information sources and no formal meta-analysis was provided for these conclusions.

Campone et al (2005)[52]
Recent publication of the final results from six clinical trials (four trials with paclitaxel and two trials with docetaxel) which demonstrate the benefits of adding taxanes in the adjuvant setting, in terms of DFS and OS in patients presenting a breast cancer with node involvement were reviewed. No systematic review criteria are given and no formal meta-analysis performed. Additional trials include PACS 01 and BCRIG 001.

Overall it was concluded that the trials demonstrate that when administered in a sequential or concomitant manner, taxanes decrease the risk of relapse and death. However a number of differences between the trials were highlighted i.e characteristics of the patients at inclusion, tamoxifen delivery and dosage-intensity of the paclitaxel treatment which could affect the strength of such a conclusion. In terms of tolerance the trials were reported to show an overall increase in haematological toxicity with the sequential regimen being less toxic in terms of neutropenia and congestive heart failure. The review suggested that the sequential schedule will most probably be favoured to the detriment of the concomitant schedule for reasons of tolerance and respect of dose-density.

Piccart et al (2005)[53]
Inclusion criteria consisted of taxane trials which provided the latest information on long-term side effects and 5-year benefits which were published after the 2003 St. Gallen consensus panel. Additional trials include PACS 01 and BCRIG 001.

No detailed search criteria are given and no formal meta-analysis provided. Following the St. Gallen consensus panel two families of chemotherapy regimes were recognised; “standard efficacy” (CMF or AC) or “superior efficacy” (FA(E)C, CA(E)F, A(E) and the anthracycline-taxane-based regimens). Whilst no particular regimen in this second group showed a clear benefit in terms of survival compared to the other, the associated complexity, toxicity and cost of these regimens were highlighted in the trials reviewed. Practical recommendations to physicians which suggest weighing the risks and benefits of these “superior efficacy” regimens for each individual patient whilst also taking into account the patients preference are given. Compared with 2003 data, the indications for using anthracycline and taxane-based regimens were higher particularly for women with ER-absent or low-ER tumours or those showing other aggressive biological features. Preference was recommended to be given to regimens which had 5 year follow –up, i.e. AC → paclitaxel or docetaxel, FEC→ docetaxel and TAC. So far, none of these treatment regimens were reported to be associated with an increased risk of leukaemia, myelodysplastic syndrome or congestive heart failure. It was noted that long-term functional cardiac assessment and cognitive function assessment were still lacking. The authors concluded that “superior efficacy” anthracycline-based regimes, without taxanes, remain an acceptable standard of care.

Smith and Chua (2006)[54]

This article is adapted from the 3rd edition of the ABC of Breast Diseases and although it is not a systematic review it does examine the evidence for chemotherapy regimens in early breast cancer treatment. Two trials, in which patients with node positive cancer were enrolled, (CALGB 9344 and NSABP-B-28) show a small but significant benefit in disease free survival following sequential paclitaxel after anthracycline chemotherapy, but only one of the trials showed survival benefit. Docetaxel, when given in combination rather than sequentially with anthracyclines, showed a 6% five year survival advantage over anthracyclines alone. The results of one trial examining accelerated or dose dense chemotherapy are reviewed. It was shown that accelerated twice-weekly doxorubicin and cyclophosphamide for four cycles followed by paclitaxel for four cycles improved disease free survival and overall survival over the same eight courses given conventionally at three-weekly intervals. It is noted that taxanes have as of yet not been shown to benefit women with node negative cancer. In addition, the shortened duration of adjuvant treatment associated with accelerated chemotherapy will probably be of interest to patients.

It is concluded that further trials are needed. Interestingly trials which explore the use of trastuzumab as adjuvant treatment in HER2 positive breast cancer are also reviewed. Substantial improvement in disease free survival and overall survival is seen when trastuzumab is given as adjuvant treatment in combination with paclitaxel and docetaxel in patients with metastatic disease. Additional trials included are the BCRIG 001 Study.

Appendix 10 - Review of International Guidelines submitted in part C of the BMS submission

Following primary treatment with lumpectomy or total mastectomy and surgical grading of disease severity, radiotherapy is recommended in all axillary node status breast cancers (except following total mastectomy with negative axillary nodes and tumour < 5 cm and margins > 1 mm).[32] Sub classification of breast cancers into hormone responsiveness (expression or non-expression of steroid hormone receptors) and overexpression or non-overexpression of the HER-2/*neu* gene is also discussed as a determinant of disease progression.[32-34]

Adjuvant hormonal therapy should be considered in all hormone responsive disease.[33] Hormonal therapy is based on pre or postmenopausal status, with premenopausal women typically receiving 2-3 years of tamoxifen ± ovarian suppression or ablation and postmenopausal women typically receiving tamoxifen for 2-3 years or 4.5-6 years or anastrozole or letrozole for 5 years.[32]

Chemotherapy should be considered in hormone non-responsive disease if tumour size is ≤ 0.5 cm or 0.6 – 1 cm.[32] The choice of which particular chemotherapy regimen to use is often based on patient preference and physician training.

Adjuvant chemotherapy should be considered in either hormone responsive and non-responsive disease if tumour size is > 1 cm or is node positive (one or more metastasis > 2 mm to one or more ipsilateral axillary lymph nodes).[32]
In both hormone responsive and non-responsive breast cancer, adjuvant chemotherapy should be combined with trastuzumab if HER-2/*neu* is overexpressed.[32]

Previous NCCN guidelines indicate the use of paclitaxel in non-trastuzumab containing regimens for HER-2/*neu* non-overexpressed disease.

Intermediate risk patients

- FEC
- AC (× 4)
- TAC with filgrastim support
- A→CMF
- CMF
- AC (× 4) + sequential paclitaxel (× 4) with filgrastim support
- FEC→T

High risk patients

- CAF or FEC or CEF
- AC (× 4)
- TAC with filgrastim support
- A→CMF
- AC (× 4) + sequential paclitaxel (× 4) with filgrastim support
- FEC→T

Intermediate risk patients are defined as node negative, age <35 years with HER-2/*neu* overexpressed or node positive (1-3 involved nodes) with HER-2/*neu* non-overexpressed. High risk patients are defined as node positive (1-3 involved nodes) and HER-2/*neu* overexpressed or node positive (4 or more involved nodes).[34]

Guideline updates in 2006 now suggest an additional role for paclitaxel in trastuzumab containing regimens for breast cancer which is HER-2/*neu* overexpressed.[32]

Appendix 10. Search strategies used to identify previously published economic evaluations

This search has been a four-stage process. A similar unfocused strategy was used in all databases to ensure all potentially relevant searches were included in the search.

1. **Search in NHS EED (NHS Economic Evaluation Database)**

This includes economic evaluations and cost studies that have been identified in Medline, Embase, Cinahl and (previously) Current Contents since 1995, when the database was set up. The admin database (Cairs T) was searched so that all studies considered for the NHS EED database were included.

NHS EED (T system)
Limit n
S (taxane$ or paclitaxel or docetaxel or taxol or taxotere) (112)
S breast (1163)
S s1 and s2 (32)

2. **Search in OHE HEED (Health Economic Evaluations Database)**

This includes economic evaluations and cost studies that have been identified in Medline and Embase, and through hand-searching of around 50 journals.

(Taxane* or paclitaxel or docetaxel or taxol or taxotere) AND breast (37)

3. **Search in Medline (Silverplatter) for European studies since 2003**

European studies have not been included in NHS EED since 2003 (since the establishment of EuroNEED) so additional searches were done to ensure that all relevant European studies were captured.

1. economics / all SUBHEADINGS in MJME,MIME
2. explode "costs and cost analysis" / all SUBHEADINGS in MJME,MIME
3. economic value of life / all SUBHEADINGS in MJME,MIME
4. economics dental / all SUBHEADINGS in MJME,MIME
5. explode "economics hospital" / all SUBHEADINGS in MJME,MIME
6. economics medical / all SUBHEADINGS in MJME,MIME
7. economics nursing / all SUBHEADINGS in MJME,MIME
8. economics pharmaceutical / all SUBHEADINGS in MJME,MIME
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8

10. (econom* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*) in ti,ab
11. (expenditure* not energy) in ti,ab
12. (value near1 money) in ti,ab
13. budget* in ti,ab
14. #10 or #11 or #12 or #13
15. #9 or #14
16. letter in pt
17. editorial in pt
18. historical-article in pt
19. #16 or #17 or #18
20. #15 not #19
21. ANIMALS in TG
22. HUMANS in TG
23. #21 not (#21 and #22)
24. #20 not #23
25. (metabolic near cost) in ti,ab
26. ((energy or oxygen) near cost) in ti,ab
27. #24 not (#25 or #26)
28. (catalan or danish or dutch or finnish or french or german or italian or norwegian or portugese or spanish or swedish) in la
29. (austria or belgium or france or luxembourg or netherlands or switzerland or germany or denmark or finland or iceland or norway or sweden or italy or portugal or spain) in ad
30. (austria / all SUBHEADINGS in MJME,MIME) or (belgium / all SUBHEADINGS in MJME,MIME) or (finland / all SUBHEADINGS in MJME,MIME) or (france / all SUBHEADINGS in MJME,MIME) or (germany / all SUBHEADINGS in MJME,MIME)
31. (italy / all SUBHEADINGS in MJME,MIME) or (luxembourg / all SUBHEADINGS in MJME,MIME) or (netherlands / all SUBHEADINGS in MJME,MIME) or (portugal / all SUBHEADINGS in MJME,MIME) or (scandinavia / all SUBHEADINGS in MJME,MIME)
32. (denmark / all SUBHEADINGS in MJME,MIME) or (norway / all SUBHEADINGS in MJME,MIME) or (sweden / all SUBHEADINGS in MJME,MIME) or (spain / all SUBHEADINGS in MJME,MIME) or (switzerland / all SUBHEADINGS in MJME,MIME)
33. #28 or #29 or #30 or #31 or #32

34. (mexico or costa rica or el salvador or guatemala or honduras or nicaragua or panama or argentina or bolivia or brazil or chile or colombia or ecuador or paraguay or peru or uruguay or Venezuela) in ad
35. (canada or united states or united kingdom or great britain or ireland or australia or new zealand) in ad
36. (mexico / all SUBHEADINGS in MJME,MIME) or (costa rica / all SUBHEADINGS in MJME,MIME) or (el salvador / all SUBHEADINGS in MJME,MIME) or (guatemala / all SUBHEADINGS in MJME,MIME) or (honduras / all SUBHEADINGS in MJME,MIME)
37. (nicaragua / all SUBHEADINGS in MJME,MIME) or (panama / all SUBHEADINGS in MJME,MIME) or (argentina / all SUBHEADINGS in MJME,MIME) or (bolivia / all SUBHEADINGS in MJME,MIME) or (brazil / all SUBHEADINGS in MJME,MIME)
38. (chile / all SUBHEADINGS in MJME,MIME) or (colombia / all SUBHEADINGS in MJME,MIME) or (ecuador / all SUBHEADINGS in MJME,MIME) or (paraguay / all SUBHEADINGS in MJME,MIME) or (peru / all SUBHEADINGS in MJME,MIME) or (uruguay / all SUBHEADINGS in MJME,MIME)
39. (venezuela / all SUBHEADINGS in MJME,MIME) or (canada / all SUBHEADINGS in MJME,MIME) or (united states / all SUBHEADINGS in MJME,MIME) or (united kingdom / all SUBHEADINGS in MJME,MIME) or (great britain / all SUBHEADINGS in MJME,MIME)
40. (ireland / all SUBHEADINGS in MJME,MIME) or (australia / all SUBHEADINGS in MJME,MIME) or (new zealand / all SUBHEADINGS in MJME,MIME)
41. #34 or #35 or #36 or #37 or #38 or #39 or #40
42. #33 not #41
43. #27 and #42
44. #43 and (UD = 20030602-20051115)
45. explode "Taxoids"/ all subheadings
46. (taxane* or paclitaxel or docetaxel or taxol or taxotere) in ti,ab
47. #45 or #46
48. explode "Breast-Neoplasms"/ all subheadings
49. breast in ti,ab
50. #48 or #49

4. Search in Embase (Ovid) for European studies since 2003

European studies have not been included in NHS EED since 2003 (since the establishment of EuroNEED) so additional searches were done to ensure that all relevant European studies were captured.

1. Health Economics/
2. exp Economic Evaluation/
3. exp Health Care Cost/
4. exp PHARMACOECONOMICS/
5. 1 or 2 or 3 or 4
6. (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
7. (expenditure$ not energy).ti,ab.
8. (value adj2 money).ti,ab.
9. budget$.ti,ab.
10. 6 or 7 or 8 or 9
11. 5 or 10
12. letter.pt.
13. editorial.pt.
14. note.pt.
15. 12 or 13 or 14
16. 11 not 15
17. (metabolic adj cost).ti,ab.
18. ((energy or oxygen) adj cost).ti,ab.
19. ((energy or oxygen) adj expenditure).ti,ab.
20. 17 or 18 or 19
21. 16 not 20
22. exp ANIMAL/
23. exp animal experiment/
24. Nonhuman/
25. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh.
26. 22 or 23 or 24 or 25
27. exp human/
28. exp human experiment/
29. 27 or 28
30. 26 not (26 and 29)
31. 21 not 30
32. (cat or dan or dut or fre or ger or ita or nor or por or spa or swe).lg.
33. austria/ or belgium/ or benelux/ or france/ or luxembourg/ or netherlands/ or switzerland/ or germany/ or denmark/ or faroe islands/ or finland/ or greenland/ or iceland/ or norway/ or sweden/ or italy/ or portugal/ or spain/

34. (austria or belgium or france or luxembourg or netherlands or switzerland or germany or denmark or finland or iceland or norway or sweden or italy or portugal or spain).in.
35. 32 or 33 or 34
36. mexico/ or belize/ or costa rica/ or el salvador/ or guatemala/ or honduras/ or nicaragua/ or panama/ or argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or paraguay/ or peru/ or uruguay/ or venezuela/ or canada/ or united states/ or united kingdom/ or ireland/ or "australia and new zealand"/
37. (mexico or costa rica or el salvador or guatemala or honduras or nicaragua or panama or argentina or bolivia or brazil or chile or colombia or ecuador or paraguay or peru or uruguay or venezuela or canada or united states or united kingdom or ireland or australia or new zealand).in.
38. 36 or 37
39. 35 not 38
40. (2003$ or 2004$ or 2005$ or 2006$).em.
41. 31 and 40
42. 41 and 39
43. exp Taxoids/
44. (taxane$ or taxoid$).ti,ab.
45. Paclitaxel.ti,ab.
46. Docetaxel.ti,ab.
47. Taxol.ti,ab.
48. Taxotere.ti,ab.
49. or/43-48
50. exp Breast Neoplasms/
51. breast.ti,ab.
52. 50 or 51
53. 49 and 52
54. 42 and 53

Results

	Results	Results after deduplication	Custom 4 field search term
NHS EED	32	27	NHS EED
HEED	37	37	HEED
Medline	10	5	Medline
Embase	11	11	Embase Ovid
TOTAL		**65**	

Appendix 11. Quality checklist of manufacturer's submission

Study question		**Comments**
1. Costs and effects examined	✓	
2. Alternatives compared	✓	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	✓	
Selection of alternatives		
4. All relevant alternatives are compared (including do-nothing if applicable)	×	Study does not include usual care in the NHS or other relevant comparators
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	✓	
6. The rationale for choosing the alternative programmes or interventions compared is stated	×	No rationale is provided for the inclusion or exclusion of comparators
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed.	✓	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	✓	
10. Effectiveness data from RCT or review of RCTs	✓	
11. Potential biases identified (especially if data not from RCTs)	×	Potential bias exists due to the lack of systematic review. Also due to the poor reporting of toxicity data.
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	
Costs		
13. All the important and relevant resource use included	×	Omits pre-medication costs for paclitaxel
14. All the important and relevant resource use measured accurately (with methodology)	×	Not enough data reported on methods used to derive health state costs
15. Appropriate unit costs estimated (with methodology)	×	A number of technical errors in calculation of unit costs. Some unjustified assumptions used in calculating chemotherapy administration costs.
16. Unit costs reported separately from resource use data	✓	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion.	✓	
Benefit measurement and valuation		

19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs, etc.)	✓	
20. Methods to value health states and other benefits are stated (e.g. time trade off)	✓	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, health care professionals etc.)	✓	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	✓	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	×	No justification provided for choice of source of many input parameters
24. All model outputs described adequately.	✓	
Discounting		
25. Discount rate used for both costs and benefits	✓	
26. Do discount rates accord with NHS guidance (3.5% for benefits; 3.5% for costs)?	✓	
Allowance for uncertainty		
Stochastic analysis of patient-level data	NA	
27. Details of statistical tests and confidence intervals are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. confidence interval around incremental cost-effectiveness ratio (ICER), cost-effectiveness acceptability curves).	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	NA	
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	✓	
31. Is second-order uncertainty (uncertainty in means) included rather than first order (uncertainty between patients)?	✓	
32. Are the probability distributions adequately detailed and appropriate?	✓	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data).	✓	
Deterministic analysis	✓	
34. The approach to sensitivity analysis is given (e.g. univariate, threshold analysis etc)	✓	
35. The choice of variables for sensitivity analysis is justified	×	
36. The ranges over which the variables are varied are stated	✓	

Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	×	
38. Major outcomes are presented in a disaggregated as well as aggregated form	✓	
39. Applicable to the NHS setting	✓	

Appendix 12. Limitations identified in the manufacturer's submission and potential actions that could address each item

Feature of model	**Implication**	**Potential action(s)** **see section 6 of model critique for corrections*
<u>Deviations from Reference Case</u> Model considers broad patient population without sub-group analyses.	Important differences in baseline risk between sub-groups not represented. The average cost-effectiveness in the broad patient population may conceal wide variation between sub-groups.	Conduct sub-group analyses based on prognostic risk factors such as number of involved nodes, tumour size and oestrogen-receptor status.
Model does not incorporate all relevant comparators.	Standard care in the NHS not represented so ICER may not reflect cost-effectiveness of paclitaxel to the NHS.	Include treatment arms for additional comparators such as extended AC (6 cycles), FAC, FEC and licensed use of docetaxel.
No systematic review to inform any model parameters.	Model based on selective use of available data. Potential bias from excluding relevant studies.	Perform systematic reviews.
Health state descriptions not based on validated generic instrument.	Utility values used in model are high compared to UK EQ-5D population norms in the same age group, and do not deteriorate as the hypothetical cohort ages. Model results may overestimate QALYs gained.	Use available utility estimates to calculate the relative decrement in utility associated with each health state, and then apply this to age-specific UK population norms.
<u>Technical errors</u> Mistake in calculating relative risks for toxicity.	Underestimates toxicity on AC-taxane arms. Bias in favour of taxane therapy.	Add in costs of G-CSF and hospitalising toxicity while on AC to all AC-taxane arms.* Or obtain accurate information on rates of neutropenia for AC vs AC-P3 from CALGB 9344 or an alternative source.
Omitted administration cost of AC from all AC-taxane arms.	Underestimates cost of AC-taxane arms. Bias in favour of taxane therapy.	Add in cost of first 4 cycles AC to all AC-taxane arms.*
Dose of doxorubicin lower than that used in trials.	Cost of AC underestimated. Affects all arms equally.	Change dose from 50mg/m^2 to 60mg/m^2.*
Mis-specified Dirichlet distribution for location of recurrence on AC.	Overestimates number of regional and distant recurrences on AC. Bias in favour of taxane therapy.	Correct mistake in formula for Dirichlet distribution.*
Unit cost of 100mg/m^2 docetaxel does not match BNF 50	Underestimates cost of docetaxel dosed at 100mg/m^2. Bias in favour of strategy AC-D3.	Correct cost from £1009.80 to £1232.25 (2x534.75+162.75).*
<u>Modelling assumptions</u> Cost of generic paclitaxel used	The analysis is relevant to the assessment of generic paclitaxel, and not the manufacturer's product Taxol®.	If the purpose is to assess the cost-effectiveness of Taxol® (as opposed to generic paclitaxel) then its unit cost should be applied.

Cost of pre-medication for paclitaxel and docetaxel omitted.	Underestimates cost of taxanes. Bias in favour of taxane therapy.	Incorporate cost of pre-medication into model. Paclitaxel pre-medication cost £3.80 per cycle and incurs additional 1hr administration. Docetaxel pre-medication cost £7.68 per cycle with no administration costs.
Cost of death due to breast cancer included but not cost of death due to other causes.	Cost of death due to other causes unlikely to be zero. Bias in favour of death due to other causes.	Explore incorporating cost of death due to other causes (or omitting cost of death due to breast cancer) in a sensitivity analysis.
Cost of outpatient visit used for 1hr administration, and adjusted down for additional hours.	Cost of outpatient visit unlikely to represent cost of 1hr administration or be suitable for adjustment. Model administration cost may not reflect cost to NHS.	Obtain additional evidence to support assumption or find more appropriate source for unit cost.
Location of recurrence differs between AC and AC-taxane.	Model results incorporate treatment effect on site of recurrence as well as risk of recurrence. Could potentially just be random variation.	Explore making location of recurrence same for all treatment strategies in a sensitivity analysis.*
Utility while on treatment same for all treatment strategies.	Differential health dis-benefits of toxicity while receiving different types of chemotherapy not represented in model results. Potential bias in favour of more toxic therapies.	Obtain additional evidence on utility while receiving treatment for AC, paclitaxel and docetaxel.
Lifetime treatment effect.	This is a strong assumption with little supportive evidence provided.	Explore alternative assumptions about length of treatment effect in a sensitivity analysis.* Obtain additional evidence on validity of assuming lifetime treatment effect.

Appendix 13. Sets of patient characteristics entered into Adjuvant! Online

Base-case:

Adjuvant Characteristics:	
Age	50
Comorbidity	Average for age
ER Status	Positive
Tumour Grade	Undefined
Tumour Size	2.1-3
Positive Nodes	4-9
Hormone	Tamoxifen

Low-risk:

Adjuvant Characteristics:	
Age	50
Comorbidity	Average for age
ER Status	Positive
Tumour Grade	Grade 1
Tumour Size	0.1 - 1.0cm
Positive Nodes	1-3
Hormone	Tamoxifen

High-risk:

Adjuvant Characteristics:	
Age	50
Comorbidity	Average for age
ER Status	Negative
Tumour Grade	Grade 3
Tumour Size	> 5.0cm
Positive Nodes	> 9
Hormone	Tamoxifen