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A Takeda,* E Loveman, P Harris, D Hartwell and K Welch

Southampton Health Technology Assessments Centre (SHTAC), University of Southampton, UK

*Corresponding author

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The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

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The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

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Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/55/01. The protocol was agreed in October 2007. The assessment report began editorial review in April 2008 and was accepted for publication in May 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.



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# Abstract

## Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review

A Takeda,* E Loveman, P Harris, D Hartwell and K Welch

Southampton Health Technology Assessments Centre (SHTAC), Southampton, UK

*Corresponding author

**Objectives:** To identify the expected delay between publication of conference abstracts and full publication of results from trials of new anti-cancer agents for breast cancer and to identify whether there are any apparent biases in publication and reporting.
**Data sources:** Major electronic databases were searched to identify randomised controlled trials (RCTs) of the selected interventions for the treatment of breast cancer.
**Review methods:** A systematic review was conducted according to standard methods. Data were extracted from the included studies using a predesigned and piloted data extraction template.
**Results:** Six anti-cancer treatments for breast cancer were included in the review: docetaxel, paclitaxel, trastuzumab, gemcitabine, lapatinib and bevacizumab. The literature searches generated 1556 references, from which 71 publications were retrieved and screened for inclusion. Screening identified 41 publications of 18 RCTs with at least one arm of treatment meeting the inclusion criteria for the review. Of the 18 included RCTs, only four publications (from three RCTs) reported the same outcomes in both an abstract and a full publication. Time between the abstract and full publication was 5 months in two cases, 7 months in one case and 19 months in one case (overall mean delay = 9 months). Eleven trials were identified that have not currently published in a full publication the data presented in an abstract or conference proceeding. The duration between publication of the abstracts and the end of August 2007 varied from 3 months to 38 months (mean delay 16.5 months). The longest delays in publication were for trials investigating gemcitabine (38 months) or bevacizumab (33 months). Observational analysis of the published and unpublished trials did not indicate any particular biases in terms of whether positive results were more likely to be fully published than non-significant ones.
**Conclusions:** It was surprising that only three of the 18 relevant RCTs had one or more full papers that reported the same outcome measures (and stage of analysis) as an earlier conference abstract. However, a limitation of this review is the small number of studies included. With a larger sample size than that in the present report, investigation into the effect of publication delay on decision-making might be feasible. Future research should include extension of this work to other anti-cancer drugs and investigation into the reasons for lengthy delays to full publication noted for some trials.

# Contents

# List of abbreviations

| | |
|---|---|
| AC | adjuvant chemotherapy |
| ASCO | American Society of Clinical Oncology |
| BNF | *British National Formulary* |
| CI | confidence interval |
| CNS | central nervous system |
| DFS | disease-free survival |
| EMeA | European Medicines Agency |
| EPAR | European Public Assessment Reports |
| ER | estrogen receptor |
| HER2+ | HER2 protein positive |
| HR | hazard ratio |
| HTA | Health Technology Assessment |
| IAUC | incremental ara under the curve |
| ITT | intention to treat |
| NICE | National Institute for Health and Clinical Excellence |
| ORR | overall response rate |
| PFS | progression-free survival |
| PP | PowerPoint presentation |
| RCT | randomised controlled trial |
| RR | relative risk |
| RT | radiotherapy |
| STA | Single Technology Appraisal |
| TDR | time to distant recurrence |
| TTP | time to (disease) progression |
| TTR | time to recurrence |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS) or it has been used only once or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# Executive summary

## Background

In recent years the development of targeted therapies has led to an increase in the number of specialised anti-cancer treatments. The National Institute for Health and Clinical Excellence (NICE) has issued guidance on many such treatments and continues to assess new drugs as they become licensed. Because the technologies are often undergoing market authorisation or have only recently been licensed, the evidence base is usually limited. Often there will be only one randomised controlled trial assessing efficacy, and this may not be fully published at the time of appraisal. It is therefore important to establish the pattern of full publications to inform the developing methodology for reviews in this fast moving area.

## Methods

The methodology for this project was constrained by the tight timescales and limited resources allowed for a short report (i.e. approximately one-third of that allowed for a full technology appraisal). A full search of existing NICE technology appraisals of anti-cancer drugs for breast cancer was undertaken by one reviewer and checked by a second. Because of time constraints these were then restricted to those that had been, or were due to be, appraised under the Single Technology Appraisal (STA) programme at NICE.

A comprehensive search strategy was developed to identify RCTs of the selected interventions for the treatment of breast cancer. The following databases were searched for published RCTs: Ovid MEDLINE; EMBASE; Database of Abstracts of Reviews of Effectiveness; Cochrane Database for Systematic Reviews; the Cochrane Central Register of Controlled Trials; and ISI Proceedings. As there were previous NICE technology assessments for many of the interventions, the searches were limited to studies published after the cut-off dates of searching in the previous publications until August 2007. Dates were therefore from 2002 for capecitabine, from 2005 for docetaxel, from 2006 for paclitaxel, and from 2000 for trastuzumab and vinorelbine. For those technologies that are currently in the process of being appraised by NICE, searches were undertaken from 5 years before the date of the first license of the technology up until August 2007.

The National Research Register and a US National Institutes of Health register (ClinicalTrials.gov) were searched to identify RCTs in progress. Websites of international conferences were also searched, from 5 years prior to the date of marketing authorisation until the present date.

Titles and abstracts of identified references were screened systematically against the inclusion criteria by one reviewer and checked by a second. Inclusion criteria detailed the patient groups, interventions and comparators defined by NICE, with no restriction on the outcome measures used. Full manuscripts of all selected citations were retrieved and assessed by one reviewer and checked by a second reviewer against the inclusion criteria. Disagreements over study inclusion were resolved by consensus or if necessary through arbitration by a third reviewer. Data were extracted from the included studies by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus, if necessary involving a third reviewer.

## Results

Six anti-cancer treatments for breast cancer were included in the review. Interventions for early breast cancer were docetaxel, paclitaxel and trastuzumab and interventions for advanced or metastatic breast cancer were gemcitabine, lapatinib and bevacizumab. The literature searches and checking of reference lists generated 1556 references, of which 71 publications were retrieved and screened for inclusion. Screening identified 41 publications of 18 RCTs with at least one arm of treatment meeting the inclusion criteria for the review.

Of the 18 included RCTs, only four publications (from three RCTs) reported the same outcomes in both an abstract and a full publication. Time between the abstract and full publications was 5

months in two cases, 7 months in one case and 19 months in one case (overall mean delay = 9 months).

Eleven trials were identified that have not currently published in a full publication the data presented in an abstract or conference proceeding. The duration between publication of the abstracts and the end of August 2007 varied from 3 months to 38 months (mean delay 16.5 months). The longest delays in publication were for trials investigating gemcitabine (38 months) or bevacizumab (33 months).

## Conclusions

Given that the searches identified 18 relevant RCTs it was rather surprising that only three of these had one or more full papers which reported the same outcome measures (and stage of analysis) as an earlier conference abstract. Observational analysis of the published and unpublished trials did not indicate any particular biases in terms of whether positive results were more likely to be fully published than non-significant ones. However, a limitation here was the small number of studies included in this report.

# Chapter 1

## Aim of the review

The aim of this short report, which was commissioned by the NIHR Health Technology Assessment (HTA) Programme, was to identify the expected delay between publication of conference abstracts and full publication of results from trials of new anti-cancer agents for breast cancer. A secondary aim of the research was to identify whether there are any apparent biases in publication and reporting.

# Chapter 2
# Background

## Description of underlying health problem and treatments

In 2004 there were 36,939 new cases of breast cancer in women in England, which represents a crude rate of 144.6 per 100,000 women.[1] Figures for Wales are available for 2005, when there were 2364 new registrations or a rate of 155.4 per 100,000 women. These figures equate to age-standardised rates per 100,000 population of 120.7 (95% CI 119.5–121.9) for England and 120.8 (95% CI 115.9–125.7) for Wales.[2] A recent review by the Office for National Statistics found a 20-year survival rate of 64% for women diagnosed with breast cancer between the ages of 50 and 69.[3]

The survival rates for breast cancer have shown great improvements since 1991 and these changes are consistent with earlier and better diagnosis and improvements in the management of breast cancer with the use of more effective treatments.[4] Recent advances in molecular oncology and sequencing of the human genome have led to greater understanding of the transformation and growth of malignant cells.[5] Drug development is therefore moving away from systemic cytotoxic chemotherapy towards novel targeted agents. These act by inhibiting specific requirements or functions of tumour cells, and some are inhibitory to normal tissues such as vascular endothelial cells.[6]

Targeted cancer therapies include several types of drugs such as monoclonal antibodies and apoptosis-inducing drugs.[7] For example, trastuzumab and lapatinib target the *HER2* gene, whereas bevacizumab targets the new blood vessels that allow tumours to grow.[8] Most targeted therapies work in the same way as antibodies made by the immune system and so they are often referred to as immune-targeted therapies.[9]

In the last 10–15 years the development of targeted therapies has led to an increase in the number of specialised anti-cancer treatments. The first monoclonal antibody to be licensed in the UK for cancer was rituximab, for high-grade lymphoma in 1998.[10] Trastuzumab was approved by the National Institute for Health and Clinical Excellence (NICE) for the treatment of advanced breast cancer in 2002[11] and for early breast cancer in 2006.[12] Other treatments for breast cancer that have emerged in recent years include antimetabolites such as gemcitabine and a microtubule-interacting agent (vinorelbine), in addition to older drugs such as the taxanes paclitaxel and docetaxel.[13] NICE has issued guidance on all of these drugs and continues to assess new treatments as they become licensed.[11,14–17] Many more targeted therapies are still in the preclinical testing stage[7] and it is likely that these will be used in combined therapy with existing cytotoxic drugs.[6] The addition of these treatments considerably increases the cost to the health service of treating the disease. In addition to the costs of the drugs themselves there may also be the costs of administration and monitoring.[18] Timely appraisal of such drugs is therefore of interest to NICE.

## Current NICE guidance for breast cancer

The NICE Single Technology Appraisal (STA) Programme aims to provide a rapid appraisal of new technologies and to allow guidance to be made available to the NHS. Chemotherapy drugs have been among the first technologies to be appraised under this new system. To make a fair and transparent appraisal of a technology it is important to evaluate all of the available evidence on its clinical effectiveness and cost-effectiveness. This should include an appraisal of the methods and results of studies. Because the technologies are often undergoing market authorisation or have only recently been licensed, the evidence base is usually limited. Often there will be only one randomised controlled trial (RCT) assessing efficacy. This may not be fully published at the time of appraisal (e.g. the recent appraisal of gemcitabine for metastatic breast cancer[17]) and may never be fully published in a peer-reviewed publication.

## Publication bias

There are four main areas of the literature relevant to this review: time to publication; publication bias in terms of direction of results; differences in results reported in abstracts and full publications; and differences in quality of reporting between abstracts and full publications.

A recently published Cochrane review[19] investigated the time lag to publication for results of clinical trials. The systematic review identified two review articles of 196 trials. The systematic review found that studies with results that statistically significantly favoured the experimental arm tended to take 4–5 years to publish, whereas trials with null or negative results (i.e. not statistically significant or statistically significantly favouring the control arm) were generally published 6–8 years following trial inception. One of the included reviews investigated AIDS trials and the other examined the time interval between the date of a trial's ethics committee approval (in Australia, between 1979 and 1988) and the date of first publication in a peer-reviewed journal. The Cochrane review[19] did not include any reviews that were specifically investigating publication bias in anti-cancer drug trials. The reviewers did identify one such study, published in 1987, but excluded it because the analysis of time to publication was not available separately for the registered and published cohorts of the trials.

Krzyzanowska and colleagues[20] conducted a survey of 510 abstracts from large phase III RCTs presented at American Society of Clinical Oncology (ASCO) meetings between 1989 and 1998. Their searches found that 26% of the trials reported in abstracts were not published in full within 5 years of presentation at a meeting. Krzyzanowska and colleagues found considerable evidence of bias in favour of full publication of significant results ($p \leq 0.05$ for primary outcome), with 81% being published within 5 years compared with 68% of studies with non-significant results. The authors followed up a number of studies that had not been published in full to find the reasons for this; the most frequent reason given was lack of time, funding or other resources.

A recent Cochrane review[21] found that only 63% of results from 79 reports (29,729 abstracts) describing randomised or controlled clinical trials are published in full. Results that showed statistical significance, favoured the experimental treatment or were from randomised or controlled clinical trials were more frequently published as full publications than other kinds of results. The review included summary reports that examined the subsequent rate of full publication of results related to biomedical science which were initially published in abstract or summary forms. The review included subject areas as far-ranging as marine biology, gastroenterology and emergency medicine. It is therefore not possible to draw any specific conclusions relating to anti-cancer therapies from this review.[21]

Other work on publication bias followed the fate of abstracts from the 1984 ASCO meeting.[22] However, this study followed up all conference abstracts to assess publication bias and did not specifically focus on time to full publication of RCTs. It is also likely that trends in publication time have changed over the past 15–20 years. A systematic review published in 2003 investigated publication bias around the acceptance rates of abstracts and their subsequent full publication.[23] The review searched for studies that identified the publication route of abstracts submitted to conferences. Again, this study was concerned with following all abstracts, not just those reporting RCTs.

Chan and colleagues[24] investigated selective reporting and publication bias in 102 randomised trials, comparing registered protocols with published reports. Their review included all clinical studies approved by an ethical committee in a particular time period, and results were not presented separately for oncology trials.

Previous HTA methodology work has assessed the link between data in conference abstracts and data in full publications. Dundar and colleagues[25,26] carried out an audit to assess the use of conference abstracts in Technology Assessment Reports compiled for NICE, and investigated whether data presented in the conference abstract differed substantially from that reported in the full publication. Rosmarakis and colleagues[27] have also documented differences in outcomes reported by abstracts and full publications in the fields of infectious diseases and microbiology.

Quality of reporting in abstracts is generally more limited than that in full papers. Hopewell and colleagues[28] identified RCTs presented at the 1992 ASCO conference and searched the literature to find corresponding full publications. The focus of their work was on identifying differences between quality of reporting in conference abstracts and quality of reporting in the later full

publications. Their results found that only 46% of the 37 identified trials had the same number of participants randomised in the abstract and full publication, and only 22% reported the same number analysed. The majority of abstracts reported results from ongoing trials, whereas 82% of the trials in the full publication were closed to follow-up. Hopewell and colleagues reported great limitations in assessing trial quality based on information presented in abstracts. Only 14% of the abstracts reported intention to treat (ITT) analysis, compared with 46% of the full publications. In an attempt to encourage more complete reporting in abstracts, Krzyzanowska and colleagues[29] modified the guidelines for the conduct and reporting of randomised trials to apply to abstracts submitted to ASCO meetings.

## Rationale for the study

With the development of new chemotherapy agents the NICE STA process is likely to see a rise in the number of drugs gaining marketing authorisation over the coming years. This will lead to a concurrent increase in the number of systematic reviews being carried out on more limited evidence bases, compared with standard technology appraisals in which more fully published trial data are usually available. NICE has already issued guidance for cases when full peer-reviewed trial data are not available.[17] It is therefore important to establish the pattern of full publications to inform the developing methodology for reviews in this fast-moving area.

# Chapter 3
# Research methods

A systematic review was conducted according to the methods outlined in a research protocol submitted to the HTA programme in July 2007. The key objective of the review was to identify the delay between publication of conference abstracts and full publication of results from RCTs of new anti-cancer agents for breast cancer. The secondary objective was to identify whether there are any apparent biases in publication and reporting.

## Identification of anti-cancer drugs for breast cancer

A full search of existing NICE technology appraisals of anti-cancer drugs for breast cancer was undertaken by one reviewer and checked by a second. This included technologies that were currently in the process of being appraised by NICE. Eleven areas of NICE guidance were identified for eight anti-cancer drugs (three drugs had guidance both for early breast cancer and for advanced/metastatic breast cancer). As such, the number of related references likely to require screening was beyond the capacity available for this short report. During this early stage of the review a decision was therefore taken to limit the number of technologies to those that had been, or were due to be, appraised under the STA programme at NICE. Such drugs tend to be appraised closer to their marketing authorisation dates than those considered under the more established Multiple Technology Appraisal (MTA) programme, and there is generally less published evidence available for them. Given the limited time available it was therefore deemed more relevant to focus on drugs appraised under these conditions, to obtain an indication of the data available and any publication bias that might affect the STA programme.

This reduced the number to six interventions that had received, or were being considered for, NICE guidance. The list of anti-cancer drugs that were identified and included is shown in *Table 1*. For each technology identified a search of the European Medicines Agency (EMeA) website, the British National Formulary (BNF) and the relevant manufacturers' websites was made to clarify the UK license details. The NICE website and the EMeA website [and the European Public Assessment Reports (EPARs) identified from the EMeA website] were also used to search for any additional information on the licensed agents and to identify RCTs of the relevant drugs.

## Search strategy

A comprehensive search strategy was developed to identify RCTs of the interventions for the treatment of breast cancer. The search strategy aimed to systematically identify all relevant studies that met the inclusion criteria given in *Table 1*. The strategy for MEDLINE, shown in Appendix 1, was modified for use in other databases. The following databases were searched for published RCTs: Ovid MEDLINE; EMBASE; Database of Abstracts of Reviews of Effectiveness (DARE); Cochrane Database for Systematic Reviews (CDSR); Cochrane Central Register of Controlled Trials; and ISI Proceedings. The National Research Register (NRR) and ClinicalTrials.gov were searched to identify RCTs in progress. Bibliographies of retrieved articles were also checked for additional studies.

Websites of international conferences such as the American Society of Clinical Oncology (ASCO) and the San Antonio Breast Cancer Symposium (SABCS) were also searched to identify relevant conference proceedings and abstracts. These were searched from 5 years prior to the date of marketing authorisation until the present date. The internet was also searched using trial names/identifiers in internet search engines such as Google.

As there were previous NICE technology assessments for many of the interventions, the searches were limited to studies published after the cut-off dates of searching in the previous publications until August 2007. Dates were therefore from 2002 for capecitabine, from 2005 for docetaxel, from 2006 for paclitaxel, and from 2000 for trastuzumab and vinorelbine. For those technologies that are currently in the process of being appraised by NICE, searches were undertaken from 5 years before the date of the first license of the technology up until August 2007.

***TABLE 1*** *Inclusion criteria for the systematic review*

| **Patients** | **Adults (over 18 years of age) with breast cancer (meeting specific disease stage criteria as appropriate)** |
|---|---|
| Interventions (alone or in combination according to licensed indications) | Gemcitabine for advanced/metastatic cancer |
| | Docetaxel for early cancer |
| | Paclitaxel for early cancer |
| | Trastuzumab for early cancer |
| | Bevacizumab for advanced/metastatic cancer |
| | Lapatinib for advanced/metastatic cancer |
| Comparator | Any, including placebo |
| Design | Randomised controlled trials |

## Study inclusion

All references identified by the literature searches were imported into a Reference Manager bibliographic database. After deleting duplicate references from the database, the title and (where available) abstract of each reference was screened systematically against the inclusion criteria reported in *Table 1*, to assess the relevance of the study for inclusion in the review. This was undertaken by one reviewer and checked by a second reviewer. Full manuscripts of all selected citations were retrieved and assessed by one reviewer and checked by a second reviewer against the inclusion criteria. Disagreements over study inclusion were resolved by consensus or if necessary through arbitration by a third reviewer.

## Inclusion criteria

The planned inclusion/exclusion criteria for the systematic review are shown in *Table 1*. There was no restriction placed on the outcome measures used at this stage of the project.

## Data extraction

Data were extracted from the included studies using a predesigned and piloted data extraction template to report information on the month and year of publication of each included study, the numbers of participants in each study arm (to allow identification of linked studies) and key outcome data from each study (see Appendix 2). Data from each study were extracted by one reviewer and checked by a second reviewer. Any disagreements were resolved by consensus, if necessary involving a third reviewer. Given the limited resources available it was only possible to extract data on the key outcomes of studies, giving preference to overall survival and any measures relating to time to disease progression. Full publications and abstracts were linked by reference to trial identifiers, trial arms, numbers of participants and any other available information. For each intervention, information on the date of any decisions made by NICE was also noted.

# Chapter 4
# Results

## Interventions included

Six anti-cancer treatments for breast cancer were included in the review. Of these treatments three were for early breast cancer and three were for advanced or metastatic breast cancer. Interventions for early breast cancer were docetaxel, paclitaxel and trastuzumab and interventions for advanced or metastatic breast cancer were gemcitabine, lapatinib and bevacizumab. Docetaxel, paclitaxel, trastuzumab and gemcitabine have been appraised by NICE; two were used as monotherapy and two were used in combination with other treatments (*Table 2*). Bevacizumab and lapatinib have appraisals in process. To keep this review relevant to the NICE appraisal process, only these applications for each of the respective drugs were used. For the two interventions that are appraisals in process we have reported all of the treatment combinations identified in the literature for bevacizumab, and restricted lapatinib to the treatment combination described in the ongoing STA. For two of the anti-cancer drugs for early breast cancer an additional indication (as per the NICE guidance) required the diagnosis to include node-positive disease (*Table 2*).

## Included RCTs

The literature searches (including checking reference lists) generated 1556 references, whose titles and abstracts were inspected. The full process is documented in the flow chart in Appendix 3. A total of 71 publications were retrieved and screened for inclusion. Of these, 30 publications were excluded according to the review criteria and 41 publications of 18 RCTs included at least one arm of treatment meeting the indications noted in *Table 2* and therefore met the inclusion criteria for the review. The breakdown in respect to each individual treatment was as follows: docetaxel, three RCTs; paclitaxel, two RCTs; trastuzumab, three RCTs; gemcitabine, two RCTs; lapatinib, three RCTs; bevacizumab, five RCTs.

## Assessment of mean time between publication of abstracts and publication of full paper

*Tables 3–8* illustrate, for each intervention, the mean time between publication of an abstract and

***TABLE 2*** *Interventions and their indications considered by NICE*[a]

| Breast cancer drug | Indications considered by NICE |
|---|---|
| Early breast cancer | |
| Docetaxel | In combination with doxorubicin and cyclophosphamide for women diagnosed with operable node-positive breast cancer |
| Paclitaxel | As monotherapy for node-positive breast cancer |
| Trastuzumab | Monotherapy as second-line treatment |
| Advanced/metastatic cancer | |
| Gemcitabine | In combination with paclitaxel |
| Lapatinib | In combination with capecitabine |
| Bevacizumab | In combination with capecitabine, docetaxel, paclitaxel or cyclophosphamide and methotrexate |

a Lapatinib and bevacizumab are currently 'appraisals in progress'; therefore, indications considered here reflect those identified in the literature for bevacizumab and the combination in NICE's scope for lapatinib.

***TABLE 3*** *Time between publication of abstract and publication of full paper for docetaxel trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***BCIRG 001*** Docetaxel plus doxorubicin and cyclophosphamide vs fluorouracil plus doxorubicin and cyclophosphamide | (1) Nabholtz[30] – Abstract (first interim analysis) | May 2002 | 37 months |
| | (2) Martin[31] – Full paper (second interim analysis) | June 2005 | |
| ***NSABP B-27*** Doxorubicin and cyclophosphamide plus docetaxel vs doxorubicin and cyclophosphamide | (1) Bear[32] – Abstract | December 2001 | These studies do not report a common outcome |
| | (2) Bear[33] – Full paper | November 2003 | |
| | (3) Bear[34] – Abstract | December 2004 | |
| | (4) Bear[35] – Full paper | May 2006 | |
| ***GEPARDUO*** Doxorubicin plus cyclophosphamide followed by docetaxel vs doxorubicin plus docetaxel | (1) von Minckwitz[36] – Abstract (reporting pathological response) | May 2002 | 5 months |
| | (2) Jackisch[37] – Full paper (reporting pathological response) | October 2002 | |
| | (3) von Minckwitz[38] – Full paper. No overall survival or time to progression data | April 2005 | Not applicable (no corresponding abstract) |
| | (4) Blohmer[39] – Abstract (analysis of overall survival data) | March 2006 | Time awaiting full publication = 18 months as of 31 August 2007 |

publication of the full paper for each trial. In some cases a trial has reported key outcomes in abstract form but no full publication of these results has been identified; for these a calculation of the mean time between publication of the abstract and the present date has been made. Some trials have reported outcomes in more than one abstract and full publication; where this has occurred careful matching of each abstract with its respective full publication was made and a calculation undertaken for each. Matching was based on the trial identifier number, where available, numbers of participants, description of treatment arms and outcomes and any other information available. Calculation of time to publication was restricted to abstracts and corresponding full papers that reported measures of overall survival or aspects of disease progression. Abstracts that only reported baseline characteristics, adverse events or quality of life scores were not included in the analysis.

As can be seen in the above tables, of the 18 included trials only three trials (GEPARDUO,[36,37] HERA[48–51] and INT 0148[42,43]) had a conference abstract and full publication sharing a common outcome (the HERA trial has two different abstracts linked to two full publications). Some of the trials reported interim analyses of their data in one publication (usually the abstract) and full analysis in another linked publication.[30,31,40,41,45,46] In others, abstracts and full publications simply reported different outcomes from the range assessed within the trial.[32–35,58,59,64,65] Therefore it would be inappropriate to include these in any overall assessment of length of time between publications.

Of the four sets of publications (from three trials) that reported the same outcomes in both an abstract and full publication, the time between the abstract and full publications was 5 months for two RCTs (docetaxel, GEPARDUO;[36,37] trastuzumab, HERA[48,49]), 7 months for one RCT (trastuzumab, HERA[50,51]) and 19 months for the other RCT (paclitaxel, INT 0148[42,43]). The mean time to full publication for these four sets of publications from the three trials is therefore 9 months.

Eleven trials were identified that have not currently published in a full publication the data presented in an abstract or conference proceeding. The duration between publication of the abstracts and the end of August 2007 varies from 3 months to 38 months (see *Table 9*). Seven trials have not published their data in full after at least 12 months

***TABLE 4*** *Time between publication of abstract and publication of full paper for paclitaxel trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***INT 0148*** Cyclophosphamide, doxorubicin and paclitaxel vs cyclophosphamide and doxorubicin | (1) Henderson[40] – Abstract (interim analysis) | May 1998 | 58 months |
| | (2) Henderson[41] – Full paper | March 2003 | |
| | (3) Sartor[42] – Abstract (subgroup analysis 1) | June 2003 | 19 months |
| | (4) Sartor[43] – Full publication (subgroup analysis 1) | January 2005 | |
| | (5) Hayes[44] – Abstract (subgroup analysis 2) | June 2006 | Time awaiting full publication = 15 months as of 31 August 2007 |
| ***NSABP B-28*** Cyclophosphamide, doxorubicin and paclitaxel vs cyclophosphamide and doxorubicin | (1) Mamounas[45] – Abstract (interim analysis) | November 2000 | 55 months |
| | (2) Mamounas[46] – Full paper | June 2005 | |
| | (3) Mamounas[47] – Abstract (adverse events) | June 2003 | Not applicable |

***TABLE 5*** *Time between publication of abstract and publication of full paper for trastuzumab trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***HERA*** Trastuzumab vs observation | (1) HERA group[48] – Abstract (interim analysis) | May 2005 | 5 months |
| | (2) Piccart-Gebhart[49] – Full paper (interim analysis) | October 2005 | |
| | (3) Smith[50] – Abstract | June 2006 | 7 months |
| | (4) Smith[51] – Full paper | January 2007 | |
| ***BCIRG 006*** Doxorubicin and cyclophosphamide plus docetaxel vs doxorubicin and cyclophosphamide plus docetaxel plus trastuzumab, vs docetaxel plus carboplatin plus trastuzumab (TCH) | (1) Slamon[52] – Abstract (first interim analysis) | December 2005 | Time awaiting full publication of most recent abstract (2) = 5 months as of 31 August 2007 |
| | (2) Slamon[53] – Abstract (second interim analysis) | April 2007 | |
| ***PACS 04*** Trastuzumab vs observation (second randomisation following adjuvant treatments) | (1) Spielmann[54] – Abstract | June 2006 | Time awaiting full publication = 15 months as of 31 August 2007 |

since the abstract data were presented, and four of these remain unpublished after 21 months or more. The data in *Table 9* are presented under subcategories of the interventions evaluated in the trials, showing that the trials for the two drugs gemcitabine and bevacizumab have the longest time without full publication.

The range of results found in this investigation makes it difficult to establish what an estimated time to publication for these sorts of drugs might be. The mean time awaiting publication for these drugs is 16.5 months, to the end of August 2007. This estimate is based on a small sample that has a large range (3–38 months). The calculation

***TABLE 6*** *Time between publication of abstract and publication of full paper for gemcitabine trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***JHQG*** Gemcitabine and paclitaxel vs paclitaxel | (1) O'Shaughnessy[55] – Abstract | June 2003 | Time awaiting full publication of most recent abstract (3) = 38 months as of 31 August 2007 |
| | (2) Albain[56] – Abstract | July 2004 | |
| | (3) Moinpour[57] – Abstract | July 2004 | |
| ***B9E-MC-S197*** Gemcitabine and paclitaxel (two groups) vs gemcitabine and docetaxel | (1) Khoo[58] – Abstract (no efficacy data) | July 2004 | Not applicable |
| | (2) Khoo[59] –Full paper | August 2006 | |

***TABLE 7*** *Time between publication of abstract and publication of full paper for lapatinib trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***NCT00078572*** Lapatinib plus capecitabine vs capecitabine | (1) Geyer[60] – Full publication (interim data) | December 2006 | Not applicable |
| | (2) Geyer[61] –Abstract | June 2007 | Time awaiting full publication (from abstract) = 3 months as of 31 August 2007 |
| ***Sherill*** Lapatinib plus capecitabine vs capecitabine | (1) Sherrill[62] – Abstract | June 2007 | Time awaiting full publication = 3 months as of 31 August 2007 |
| ***Cameron*** Lapatinib plus capecitabine vs capecitabine | (1) Cameron[63] – Abstract | December 2006 | Time awaiting full publication = 9 months as of 31 August 2007 |

does not take into account any differences in the interventions, the manufacturers or the trial sponsors and any publication bias due to positive or negative results. However, it would appear that for the majority of the trials there is at least a 12-month delay for full publication, to the end of August 2007.

## Comparison of results of abstracts and full papers

Four sets of publications from three trials (GEPARDUO,[36,37] HERA[48–51] and INT 0148[42,43]) reported the same outcome in an abstract and a full publication. Of these, only two (both sets of publications from the HERA trial[48–51]) reported data on overall survival and time to disease progression. Of the other two linked studies, one was a publication of a secondary outcome (pathological complete response[36,37]) and one was a subgroup analysis of radiotherapy delivery.[42,43] Because of the limitations of this review as a short report, these last two outcomes were not data extracted. The interim analysis of data in the HERA trial[48,49] for overall survival and for time to disease progression was the same in the abstract and the linked full publication. The 2-year follow-up analysis of data from patients receiving a years' treatment in the HERA trial[50,51] was also the same in the abstract and the corresponding full publication.

### Trials reporting interim results in abstracts and final results in full publication

Outcomes reported within linked publications in which one paper reported interim results and one reported full results have also been investigated

***TABLE 8*** *Time between publication of abstract and publication of full paper for bevacizumab trials*

| Trial identifier and interventions | Publication details and status | Date published | Estimated time delay between abstract and full paper |
|---|---|---|---|
| ***Miller***<br>Bevacizumab plus capecitabine vs capecitabine | (1) Miller[64] – Abstract (baseline data only) | December 2002 | Not applicable |
| | (2) Miller[65] – Full paper | February 2005 | |
| ***Overmoyer***<br>Bevacizumab plus docetaxel vs docetaxel | (1) Overmoyer[66] – Abstract (reports tumour size) | July 2004 | Time awaiting full publication since most recent abstract = 33 months as of 31 August 2007 |
| | (2) Overmoyer[67] – Abstract (reports tumour size) | December 2004 | |
| ***E2100***<br>Bevacizumab plus paclitaxel vs paclitaxel | (1) Miller[68] – Abstract | December 2005 | Time awaiting full publication (from abstract (1) reporting overall survival data) = 21 months as of 31 August 2007 |
| | (2) Wagner[69] – Abstract (quality of life outcomes) | December 2006 | Not applicable |
| ***Lyons***<br>Bevacizumab plus docetaxel vs docetaxel | (1) Lyons[70] – Abstract (reports tumour size) | June 2006 | Time awaiting full publication = 15 months as of 31 August 2007 |
| ***Burstein***<br>Bevacizumab plus cyclophosphamide and methotrexate vs cyclophosphamide and methotrexate | (1) Burstein[71] – Abstract (reports tumour size) | December 2005 | Time awaiting full publication = 21 months as of 31 August 2007 |

***TABLE 9*** *Length of time since publication of trial data in abstract form to the end of August 2007*

| Trial identifier | Time since abstract published | Statistical significance of trial results |
|---|---|---|
| ***Docetaxel for early breast cancer*** | | |
| GEPARDUO[39] | 18 months | Not significant |
| ***Trastuzumab for early breast cancer*** | | |
| BCIRG 006[52,53] | 5 months | Significant |
| PACS 04[54] | 15 months | No overall survival data |
| ***Gemcitabine for advanced/metastatic breast cancer*** | | |
| JHQG[55–57] | 38 months | Significant |
| ***Lapatinib for advanced/metastatic breast cancer*** | | |
| NCT00078572[60,61] | 3 months | Not significant |
| Sherrill[62] | 3 months | Significant |
| Cameron[63] | 9 months | Not reported |
| ***Bevacizumab for advanced/metastatic breast cancer*** | | |
| Lyons[70] | 15 months | Not reported |
| E2100[68,69] | 21 months | Significant |
| Burstein[71] | 21 months | Not reported |
| Overmoyer[66,67] | 33 months | Not reported |

for direction of the effect shown. Although it would not be meaningful to compare the actual results of these publications, because one is clearly published at an interim point in time, it is meaningful to consider if the direction of the results is similar. Three trials reported interim data in an abstract and final data in a full publication. Two of these were trials of paclitaxel (INT0148;[40,41] NSABP-B28[45,46]) and one was of docetaxel (BCIRG 001[30,31]). Although the docetaxel trial BCIRG001 reported a second interim analysis rather than a full final analysis, it has been included here as it reports the same outcome measures as the abstract. The full paper acknowledges that a further analysis would be required to confirm and extend their estimated 5-year survival rate.[31]

*Paclitaxel*

Data presented for overall survival in the INT0148 trial[40,41] were positive for treatment with paclitaxel in both the abstract[40] and the full results.[41] Observation of the data suggests that there was a better effect on survival at the point of the interim analysis than in the full publication (see Appendix 2 for further details). Time to disease progression was reported in the full publication. These data were not reported in the abstract, although it was stated that the addition of paclitaxel had a significant impact on disease-free survival. The NSABP-B28 trial[45,46] reported no statistically significant differences between treatment arms in survival or death at the interim analysis in the abstract.[45] There was a non-statistically significant reduction in the death rate reported in the full publication.[46] Disease-free survival in this trial was reported as not statistically significantly different at the interim (abstract) analysis but statistically significantly different (in favour of paclitaxel) at the full analysis.

*Docetaxel*

The BCIRG 001 trial[30,31] reported overall survival and time to disease progression as interim data in an abstract and full data in a peer-reviewed publication. For overall survival, the risk ratio (adjusted for node status) was not statistically significant in the abstract[30] but had reached statistical significance by the 5-year results reported in the full publication.[31] For disease-free survival, the risk ratios (adjusted for node status) presented in both the abstract and the full 5-year publication were statistically significant.

### Direction of results reporting in abstract form

Of the 11 trials that are not yet published in a full publication (see *Table 9*), only six reported overall survival or an outcome measuring time to disease progression. In the small sample of RCTs considered here, the statistical significance of results did not appear to affect the likelihood of full publication of data previously reported in a conference abstract. Indeed, four of the six trials included here reported statistically significant results. Similarly, statistical significance did not appear to influence the length of time to publication (or to the present date for unpublished studies).

## Ongoing trials

A number of trials in progress were identified in searches of the National Research Register and ClinicalTrials.gov, and these were assessed against the inclusion criteria for this review to see if they would be of relevance for any future update of this review. These trials are summarised in Appendix 4; some may be related to trials included in this review.

# Chapter 5
# Discussion

The methodology for this short report was developed with a focus on relevance to the NICE appraisal process, i.e. assessment of published RCTs. As such, we identified publications from literature searches in the same way as for a systematic review, with additional searching of websites. Other work in this area has taken a different approach, by identifying trials from registers and following up for publications,[24] or by following all abstracts from particular conferences to see when they became fully published.[20,22,28] Although these approaches are more comprehensive, time restrictions and the focus on the NICE appraisal process led us to adopt the different methodology discussed in Chapter 3.

There were 41 publications of 18 RCTs that met the inclusion criteria for this review: three RCTs for docetaxel; two for paclitaxel; three for trastuzumab; two for gemcitabine; three for lapatinib; and five for bevacizumab.

## Time to publication

The main focus of this review was the calculation of time from conference abstract to full publication for RCTs of paclitaxel, docetaxel, gemcitabine, trastuzumab, lapatinib and bevacizumab.

For docetaxel, time to full publication varied from 5 months for pathological response outcomes in the GEPARDUO trial,[37] to 37 months for publication of interim survival in another trial.[31] Overall survival for the GEPARDUO trial was published in March 2006 as a conference abstract[39] but has not yet been published in full. The other trial had two conference abstracts[32,34] and two full papers,[33,35] but these did not report the same outcome measures and so could not be compared directly.

The publication delay for paclitaxel trials tended to be longer than that for docetaxel trials, although it was difficult to compare the abstracts and full publications directly as both paclitaxel trials reported interim analyses in abstracts and final analyses in the full papers. For one trial[41] the delay between the interim analysis appearing in an abstract and the final analysis being published in a full paper was 58 months, and there was a 55-month delay in the other trial.[46] One set of subgroup analyses was published more quickly (19 months[43]), and another was still unpublished after 15 months as of August 2007.

For one of the trastuzumab trials there was only a 5-month delay between the interim analyses being published in a conference abstract and as a full paper,[49] and a 7-month delay between the abstract and full publication of the 2-year follow-up analysis of patients who received a year of treatment. However, other trials have been published only as abstracts so far, with delays of 5–21 months as of August 2007. One of the gemcitabine RCTs identified by the literature searches has not yet been published in full, despite a delay of 38 months since the most recent abstract was presented at a conference.[57] For the other identified gemcitabine trial, both a full paper and an abstract were identified, but the abstract did not present any efficacy data.

The two most recent breast cancer drugs to be in the process of NICE appraisal are lapatinib and bevacizumab. Although one full paper was identified for a lapatinib trial,[60] this only presented interim analysis. A more recent abstract of this trial[61] and two of another trial[62,63] had not been published in full as of August 2007. Only one full paper was presented for a bevacizumab trial,[65] and the only abstract linked with this presented baseline data rather than any results. None of the other four bevacizumab trials have yet been published in full, with delays in publication of between 15[70] and 33[67] months as of August 2007.

Overall, very few of the identified trials had both a conference abstract and a full publication that reported the same results. Mean time to publication for the three paclitaxel and docetaxel trials that had both an abstract and a full paper reporting the same outcome measures was 9 months. Mean time without full publication for those trials that have only published as abstracts was 16.5 months to the end of August 2007. The longest delays in publication were for trials investigating gemcitabine (38 months) or bevacizumab (33 months).

## Direction of effect

Overall survival and time to disease progression were of particular interest in this review as they are the measures most commonly used by NICE for analysis of an anti-cancer drug's effectiveness. Only three trials reported the same outcome measures in both abstracts and a full publication, and only two sets of abstracts and publications (from the HERA trastuzumab trial) reported outcomes of overall survival and time to disease progression. For the HERA trial, the overall survival and time to disease progression results were consistent between the abstracts and corresponding full publications.

Trials that published interim analysis in an abstract and final analysis in a full publication were examined separately from those discussed above. There were two paclitaxel trials and one docetaxel trial that fell into this category. One of the paclitaxel trials (INT0148) reported a positive effect on survival in both the abstract[40] and the full publication.[41] The other paclitaxel trial (NSABP B-28) reported no significant difference at either the interim analysis[45] or the final analysis.[46] Disease-free survival was reported to be statistically better with paclitaxel by the time of the final analysis[46] but not at the time of the interim analysis.[45] The docetaxel trial reported statistically significant benefits of treatment with docetaxel in terms of overall survival and time to disease progression in both the abstract and full publication. The trials were therefore consistent in the direction of effect reported in the abstracts and full publications, with the exception of disease-free survival in the NSABP B-28 trial.

Overall, it would appear that, when linkage of abstracts and full publications was possible, the results presented in the abstracts were in line with the results presented later in a full publication. It is important to note that this is based on observation of the data only (no statistical analysis was undertaken) and on a small sample of trials.

## Limitations of the report

This short report was written within a tight timescale and as such there were a number of limitations that restricted the review at key stages. It was not possible to include studies beyond those drug combinations and patient groups appraised under the NICE STA programme. This restricted the available evidence and, although it allowed us to focus on the types of published evidence available to NICE under the STA programme, it resulted in a rather small sample size. No statistical analysis was performed because of the small sample size and the short time frame for this report.

Data extraction resources were focused on the key outcomes of overall survival and disease-free survival or time to progression. These were thought to be of most relevance to the NICE review process, but consideration of other outcomes could have yielded interesting data if resources had allowed.

We calculated the mean time from abstract to full publication or to the time of writing if no full publication had occurred, i.e. the data were censored at the time of this analysis. This is a limitation of the project as mean times would be affected by the subsequent publication of full articles if the analysis were to be repeated at a later date.

# Chapter 6
# Conclusions

The aim of this short report was to identify the delay between conference abstracts and full publication of results from RCTs of new anti-cancer agents for breast cancer. The secondary aim was to identify any apparent biases in publication and reporting.

Given that the searches identified 18 relevant RCTs it was rather surprising that only three of these had one or more full papers that reported the same outcome measures (and stage of analysis) as an earlier conference abstract. The trials that had fully published their results did so within a mean time frame of 9 months, which seems reasonable. Of the trials that have not yet published in full following earlier conference presentations, a longer mean delay of 16.5 months as of August 2007 was found. There did not appear to be any particular biases in terms of whether statistically significant results were more likely to be fully published than non-significant ones. However, a limitation here is the small number of studies included in this report and the consequent lack of statistical analysis.

This report has examined the data that is publicly available, of the kind that would be included in a systematic review of the literature carried out as part of the NICE appraisal process. Docetaxel, paclitaxel and trastuzumab all had at least one full publication reporting overall survival prior to NICE guidance being issued (although the overall survival data for the HERA trial appears to have been only interim analysis). For gemcitabine, no fully published data on overall survival was published prior to NICE guidance being produced. At the time of writing, NICE had not yet issued guidance on the use of bevacizumab or lapatinib.

A further important source of evidence for the evidence review groups and NICE's appraisal committee is the manufacturer's submission. Such submissions usually contain unpublished data of trials that may be available publicly only as conference abstracts. Although the body of evidence reviewed by NICE therefore extends beyond that in the public domain, there is still the issue of whether or not such data is of the same quality as that published in peer-reviewed journals.

## Research recommendations

- Extension of this work to other anti-cancer drugs that have been through NICE's MTA or earlier technology appraisal processes. With a larger sample size than that in the present report, investigation into the effect of publication delay on decision-making might be feasible.
- Investigation into the reasons for lengthy delays to full publication noted for some trials.
- Investigation of publications appearing as 'online early', which may not appear in databases such as MEDLINE until a later date.
- Investigation of trials that publish as full papers but which do not have associated conference abstracts.

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## Contribution of authors

Andrea Takeda co-ordinated the project, developed the protocol and background, performed the inclusion screening, and drafted the report. Emma Loveman developed the protocol and background, performed the inclusion screening and data extraction, and drafted the report. Petra Harris developed the background, performed the inclusion screening and data extraction, and drafted the report. Debbie Hartwell performed the inclusion screening and data extraction, and drafted the report. Karen Welch carried out the literature search.

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# Appendix 1

## MEDLINE search strategy for gemcitabine

Other interventions used the same search strategy, with replacement of drug names. The MEDLINE strategy was adapted for the other databases searched.

| **Database and years searched** | |
|---|---|
| MEDLINE 1996–2007 | Searched 31 July 2007 |
| | 1 exp breast neoplasms/(74210) |
| | 2 (breast$adj4 (cancer$or tumo?r$or malignan$or carcinoma$or neoplasm$or oncolog$or sarcoma$or adenocarcinoma$)).ti,ab. (73935) |
| | 3 1 or 2 (90093) |
| | 4 randomized controlled trial.pt. (140941) |
| | 5 exp randomized controlled trials/(41205) |
| | 6 random allocation/(23124) |
| | 7 double blind method/(47144) |
| | 8 single blind method/(8464) |
| | 9 ((singl$or doubl$or trebl$or tripl$) adj3 (blind$or mask$)).ti,ab. (44877) |
| | 10 placebo$.ti,ab. (58048) |
| | 11 placebos/(8229) |
| | 12 random$.ti,ab. (248330) |
| | 13 or/4–12 (338240) |
| | 14 3 and 13 (7691) |
| | 15 (gemcitabine or gemcytabine or gemzar).mp. (4167) |
| | 16 14 and 15 (53) |
| | 17 limit 16 to humans (53) |
| | 18 limit 17 to yr="2006 – 2007" (8) |
| | 19 from 18 keep 1–8 (8) |
| Search dates for other drugs | |
| 2002–2007 | Capecitabine |
| 2005–2007 | Docetaxel |
| 2006–2007 | Paclitaxel |
| 2000–2007 | Vinorelbine |
| 2000–2007 | Trastuzumab |
| 5 years pre-license – 2007 | Bevacizumab |
| 5 years pre-license – 2007 | Lapatinib |

# Appendix 2

# Data extractions

## Docetaxel (Taxotere®; Sanofi-Aventis)

***TABLE 10*** *Docetaxel: data extractions from STA (early breast cancer)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***BCIRG 001*** | | | |
| Martin *et al.*, 2005[31]<br><br>Month: June<br><br>Full publication: second interim analysis (median follow-up 55 months)<br><br>Trial identifier: BCIRG 001 (Breast Cancer International Research Group) | Intervention: $n = 745$ TAC (docetaxel plus doxorubicin and cyclophosphamide)<br><br>Comparator: $n = 746$ FAC (fluorouracil plus doxorubicin and cyclophosphamide) | Overall survival: at 5 years 87% of TAC vs 81% of FAC patients, with a 30% reduction in risk of death for TAC (hazard ratio 0.70, 95% CI 0.53–0.91, $p < 0.008$)<br><br>Time to disease progression: disease-free survival at 5 years was 75% for TAC vs 68% for FAC patients, with a 28% reduction in the risk of relapse (hazard ratio 0.72, 95% CI 0.59–0.88, $p = 0.001$) for the TAC group | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery.<br><br>Decision prior to this publication: no |
| Nabholtz *et al.*, 2002[30]<br><br>Month: May<br><br>Abstract (interim analysis)<br><br>Trial identifier: BCIRG 001 | Intervention: $n = 745$ TAC (docetaxel plus doxorubicin and cyclophosphamide)<br><br>Comparator: $n = 746$ FAC (fluorouracil plus doxorubicin and cyclophosphamide)<br><br>Patients were stratified by nodes (1–3, 4+) | Overall survival: RR TAC/FAC (95% CI):<br><br>Adjusted for nodal status: 0.76 (0.54–1.07), $p = 0.11$<br><br>Unadjusted: 0.75 (0.53–1.06), $p = 0.10$<br><br>1–3 nodes: 0.46 (0.26–0.80), $p = 0.006$<br><br>4+ nodes: 1.08 (0.69–1.69), $p = 0.75$<br><br>Time to disease progression: disease-free survival RR TAC/FAC (95% CI):<br><br>Adjusted for nodal status: (first end point) 0.68 (0.54–0.86), $p = 0.0011$<br><br>Unadjusted: 0.67 (0.53–0.85), $p = 0.0008$<br><br>1–3 nodes: 0.50 (0.35–0.72), $p = 0.0002$<br><br>4+ nodes: 0.86 (0.63–1.17), $p = 0.33$ | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery.<br><br>Decision prior to this publication: no |

CI, confidence interval; RR, relative risk.

***TABLE 11*** *Docetaxel: identified fron new searches*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***NSABP B-27*** | | | |
| Bear *et al.*, 2006[35]<br><br>Month: May<br><br>Full publication (first published report)<br><br>Trial identifier: NSABP B-27 | $n = 2411$ randomised, $n = 2404$ with end point data<br><br>Group 1: $n = 802$ doxorubicin and cyclophosphamide for four cycles followed by surgery<br><br>Group 2: $n = 803$ doxorubicin and cyclophosphamide for four cycles plus docetaxel followed by surgery<br><br>Group 3: $n = 799$ doxorubicin and cyclophosphamide followed by surgery followed by docetaxel | Overall survival (reviewer reported as group population minus deaths): group 1: 645 (80%), group 2: 647 (81%); group 3: 628 (79%). No statistically significant differences between groups<br><br>Addition of docetaxel had no significant impact<br><br>Time to disease progression: no statistically significant differences between groups for DFS<br><br>Improved DFS for preoperative docetaxel but not for postoperative in patients with clinical partial response after doxorubicin and cyclophosphamide (HR = 0.71, 95% CI 0.55–0.91, $p = 0.007$) | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |
| Bear *et al.*, 2004[34]<br><br>Month: December<br><br>Abstract<br><br>Trial identifier: NSABP B-27 | $n = 2411$ randomised, no breakdown<br><br>Intervention: preoperative doxorubicin/ cyclophosphamide plus preoperative docetaxel<br><br>Comparator 1: preoperative doxorubicin/ cyclophosphamide<br><br>Comparator 2: preoperative doxorubicin/ cyclophosphamide plus postoperative docetaxel | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Results of tumour size and key characteristics | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |
| Bear *et al.*, 2003[33]<br><br>Month: November<br><br>Full publication<br><br>Trial identifier: NSABP B-27 | Intervention: $n = 805$, preoperative doxorubicin/ cyclophosphamide plus docetaxel (group 2)<br><br>Comparators: $n = 804$, preoperative doxorubicin/ cyclophosphamide (group 1); $n = 802$, preoperative doxorubicin/ cyclophosphamide plus postoperative docetaxel (group 3) | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Reports on clinical and pathological complete and partial response rates and tumour size – follow-up data may report overall survival and DFS | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |

***TABLE 11*** *Docetaxel: identified from new searches*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| Bear *et al.*, 2001[32]<br><br>Month: December<br><br>Abstract<br><br>Trial identifier: NSABP B-27 | *n* = 2500 randomised<br><br>Intervention: preoperative doxorubicin/ cyclophosphamide (group 1)<br><br>Comparators: preoperative doxorubicin/ cyclophosphamide followed by four cycles of preoperative docetaxel (group 2); preoperative doxorubicin/ cyclophosphamide followed by postoperative docetaxel (group 3)<br><br>All received tamoxifen | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>No data presented | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |
| ***GEPARDUO*** | | | |
| von Minckwitz *et al.*, 2005[38]<br><br>Month: April<br><br>Full publication (first phase of trial)<br><br>Trial identifier: GEPARDUO | Intervention: *n* = 455 randomised, doxorubicin plus docetaxel every 14 days for four cycles with filgrastim support (group 1)<br><br>Comparator (detail): *n* = 458 randomised, doxorubicin plus cyclophosphamide every 21 days followed by docetaxel every 21 days for four cycles (group 2) | Overall survival and time to disease progression: not reported<br><br>Disease progression or occurrence of new lesion detected in 14 in group 1 (3.2%) and 16 in group 2 (3.7%) | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |
| Blohmer *et al.*, 2006[39]<br><br>Month: March<br><br>Abstract (first analysis of event-free and overall survival)<br><br>Trial identifier: GEPARDUO | Intervention: *n* = 455 randomised, doxorubicin plus docetaxel every 14 days for four cycles with G-CSF (filgrastim) support (group 1)<br><br>Comparator: *n* = 458 randomised, doxorubicin plus cyclophosphamide every 21 days followed by docetaxel every 21 days for four cycles (group 2) | Overall survival: 57 deaths (group 1) vs 48 deaths (group 2) at 5-year follow-up; 5-year overall survival rates are estimated at 81.0% (group 1) vs 84.8% (group 2), log-rank $p = 0.24$<br><br>5-year event-free survival rate was 65.0% (group 1) vs 66.1% (group 2), log-rank $p = 0.66$.<br><br>Time to disease progression: not reported | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |

*continued*

***TABLE 11*** *Docetaxel: identified fron new searches (continued)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| von Minckwitz *et al.*, 2002[36]<br><br>Month: May<br><br>Abstract (second interim analysis, *n* = 395)<br><br>Trial identifier: GEPARDUO | Intervention: *n* = 198 randomised, 8-week schedule of doxorubicin (Adriamycin®, Pharmacia SpA) plus docetaxel with G-CSF (filgrastim) support (group 1); tamoxifen given simultaneously<br><br>Comparator: *n* = 197 randomised, sequential 24-week schedule of doxorubicin plus cyclophosphamide followed by docetaxel (group 2); tamoxifen given simultaneously | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>At second interim analysis there was a large difference in the pathological complete response rate of 19.5% (99% CI 10.1–28.9)<br><br>Reviewer note: presuming it is in favour of ADOC, but not specified | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |
| Jackisch *et al.*, 2002[37]<br><br>Month: October<br><br>Full paper (second interim analysis)<br><br>Trial identifier: GEPARDUO | 913 enrolled in study but for this interim analysis results on 395 randomised<br><br>Intervention: *n* = 191, four cycles of doxorubicin + docetaxel ± tamoxifen (group 1)<br><br>Comparator: *n* = 178, sequential doxorubicin/ cyclophosphamide followed by docetaxel over 24 weeks (group 2) | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Results on pathological remission and toxicity | Date: September 2006<br><br>Decision: docetaxel, when given concurrently with doxorubicin and cyclophosphamide (the TAC regimen) in accordance with its licensed indication, is recommended as an option for the treatment of women with early node-positive breast cancer following surgery<br><br>Decision prior to this publication: no |

ADOC, adriamycin + docetaxel; CI, confidence interval; DFS, disease-free survival; G-CSF, granulocyte-colony stimulating factor; HR, hazard ratio.

## Paclitaxel (Taxol®, Bristol-Myers Squibb; Paxene®, Norton Healthcare)

***TABLE 12*** *Paclitaxel: from STA (early breast cancer)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***INT 0148 (intergroup trial) and CALGB-9344*** | | | |
| Henderson *et al.*, 2003[41]<br><br>Month: March<br><br>Full publication<br><br>Trial identifier: INT 0148 (intergroup trial) and CALGB-9344 | $n = 3170$ randomised; $n = 3121$ received treatment<br><br>First randomisation to one of three doses of doxorubicin and cyclophosphamide, second randomisation to receive or not receive paclitaxel<br><br>Intervention: total $n = 1590$, cyclophosphamide plus escalating dose of doxorubicin for four cycles ($n = 1060$, 60 mg/m$^2$; $n = 1053$, 75 mg/m$^2$; $n = 1057$, 90 mg/m$^2$) followed by four cycles of paclitaxel (group 1)<br><br>Comparator: total $n = 1580$, cyclophosphamide and escalating dose of doxorubicin for four cycles ($n = 1060$, 60mg/m$^2$; $n = 1053$, 75mg/m2; $n = 1057$, 90mg/m$^2$) (group 2) | Overall survival (±SE): 77% (±1) for group 2 vs 80% (±1) for group 1 at 5 years; 68% (±2) for group 2 vs 74% (±2) for group 1 at 7 years<br><br>Time to disease progression: hazard reductions from adding paclitaxel were 17% for recurrence ($p = 0.0023$ adjusted, $p = 0.0011$ unadjusted) and 18% for death ($p = 0.0064$ adjusted, $p = 0.0098$ unadjusted)<br><br>At 5 years, disease-free survival (±SE) was 65% (±1) for group 2 vs 70% (±1) for group 1; at 7 years, disease-free survival (±SE) was 58% (±2) for group 2 vs 64% (±2) for group 1 | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |
| Henderson *et al.*, 1998[40]<br><br>Month: May<br><br>Abstract (first interim analysis)<br><br>Trial identifier: INT 0148/ CALGB-9344 | $n = 3170$ randomised<br><br>First randomisation to one of three doses of doxorubicin and cyclophosphamide, second randomisation to receive or not receive paclitaxel<br><br>Intervention: cyclophosphamide plus doxorubicin – 60, 75 or 90 mg/m$^2$ – followed by four cycles of paclitaxel (group 1)<br><br>Comparator: cyclophosphamide plus doxorubicin – 60, 75 or 90 mg/m$^2$ (group 2) | Overall survival: no differences in overall survival related to dose of doxorubicin; paclitaxel reduced death rate by 26%<br><br>Time to disease progression: not reported<br><br>Paclitaxel reduced recurrence rate by 22%<br><br>Addition of paclitaxel significantly improved overall survival and DFS; no *p*-values, etc. given<br><br>Toxicity also reported | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |

*continued*

***TABLE 12*** *Paclitaxel: from STA (early breast cancer) (continued)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| Sartor *et al.*, 2003[42]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: CALGB-9344 (INT 0148)<br><br>Subgroup analysis | $n = 1111$, data for $n = 996$<br><br>Intervention: four cycles of doxorubicin/Cytoxan® (Neosar; cyclophosphamide) – 60, 75 or 90 mg/m$^2$ – followed by four cycles of paclitaxel<br><br>Comparator: four cycles of doxorubicin/Cytoxan (cyclophosphamide) – 60, 75 or 90 mg/m$^2$ | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Data for radiotherapy delivery only | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |
| Hayes *et al.*, 2006[44]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: CALGB-9344<br><br>Subgroup analysis | $n \sim 2800$, two sets of 750 patients randomly selected – set 1 to test hypothesis, set 2 for validation<br><br>Intervention: four cycles of doxorubicin/cyclophosphamide – 60, 75 or 90 mg/m$^2$ – followed by four cycles of paclitaxel<br><br>Comparator: four cycles of doxorubicin/cyclophosphamide – 60, 75 or 90 mg/m$^2$ | Overall survival: not reported, refers to original publication<br><br>Time to disease progression: not reported<br><br>Only for both sets combined, significant differences in 5-year DFS rates (95% CI) for paclitaxel vs no paclitaxel by HER2 and estrogen receptor (ER)<br><br>Benefits of adding paclitaxel greater for HER2+ tumours with ER+ | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |
| Sartor *et al.*, 2005[43]<br><br>Month: January<br><br>Full publication<br><br>Trial identifier: INT 0148/ CALGB-9344<br><br>Subgroup analysis | Subgroups: mastectomy patients treated with radiotherapy (RT), mastectomy patients not treated with RT and patients with breast-conserving therapy and RT; also subgroups by number of nodes<br><br>Intervention AC-T: four cycles of doxorubicin/cyclophosphamide – 60, 75 or 90 mg/m$^2$ – followed by four cycles of paclitaxel<br><br>Comparator: doxorubicin/ cyclophosphamide – 60, 75 or 90 mg/ m$^2$ | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Results on 5-year cumulative incidence of isolated locoregional recurrence | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |

***TABLE 12*** *Paclitaxel: from STA (early breast cancer)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***NSABP B-28*** | | | |
| Mamounas *et al.*, 2005[46]<br><br>Month: June<br><br>Full publication<br><br>Trial identifier: NSABP B-28 (national surgical adjuvant breast and bowel cancer project) | Intervention: *n* = 1531, doxorubicin plus cyclophosphamide plus paclitaxel (group 1)<br><br>Comparator: *n* = 1529, doxorubicin plus cyclophosphamide (group 2) | Overall survival: a non-statistically significant 7% reduction in death rate with addition of paclitaxel (RR 0.93, 95% CI 0.78–1.12, *p* = 0.46); 5-year overall survival rate 85% (±2%) for both groups<br><br>Time to disease progression: addition of paclitaxel significantly reduced the risk of a DFS event by 17% (RR 0.83, 95% CI 0.72–0.95, *p* = 0.006); 5-year DFS 76% (±2%) for group 1 vs 72% (±2%) for group 2 | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |
| Mamounas *et al.*, 2003[47]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: NSABP B-28 | Randomised: *n* = 3060<br><br>Intervention: doxorubicin plus cyclophosphamide plus paclitaxel<br><br>Comparator: doxorubicin plus cyclophosphamide | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>(As of 18 December 2002, 472 deaths and 827 events reported) | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |
| Mamounas 2000[45]<br><br>Month: November<br><br>Abstract<br><br>Trial identifier: NSABP B-28 (interim analysis) | Randomised: *n* = 3060<br><br>Intervention: four cycles of doxorubicin and cyclophosphamide followed by four cycles of paclitaxel (group 1)<br><br>Comparator: four cycles of doxorubicin and cyclophosphamide (group 2) | Overall survival: no statistically significant difference between arms for survival or death (deaths: 113 group 2/136 group 1; relative risk 1.0, 95% CI 0.78–1.27, *p* = 0.98). Estimated survival at 36 months is 92% group 2 and 90% group 1<br><br>Time to disease progression: no statistically significant difference between arms for DFS (events: 282 group 2/269 group 1; relative risk 0.93, 95% CI 0.78–1.10, *p* = 0.38). Estimated DFS at 36 months is 81% for both arms | Date: September 2006<br><br>Decision: paclitaxel, within its licensed indication, is not recommended for the adjuvant treatment of women with early node-positive breast cancer<br><br>Decision prior to this publication: no |

CI, confidence interval; DFS, disease-free survival.

## Trastuzumab

***TABLE 13*** *Trastuzumab: from STA (early breast cancer)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***HERA*** | | | |
| Piccart-Gebhart *et al.*, 2005[49]<br><br>Month: October<br><br>Full publication (interim analysis – median 1-year follow-up)<br><br>Trial identifier: HERA (BIG 01–01) | Intervention group 1: $n = 1694$, 2 years of trastuzumab – not reported here<br><br>Intervention group 2: $n = 1694$, 1 year of trastuzumab<br><br>Comparator: $n = 1693$, observation | Overall survival: 96.0% trastuzumab group vs 95.1% observation group; hazard ratio 0.76 (95% CI 0.47–1.23, $p = 0.26$)<br><br>Time to disease progression: DFS 127 events in the trastuzumab group vs 220 events in the observation group; hazard ratio for risk of an event in trastuzumab group vs observation group 0.54 (95% CI 0.43–0.67, log-rank test $p < 0.0001$) – equivalent to DFS of 8.4% points at 2 years (95% CI 2.1–14.8)<br><br>Hazard ratio for time to distant recurrence for trastuzumab vs observation 0.49 (95% CI 0.38–0.63, $p < 0.0001$) – reduced rate of recurrence approximately 50% higher for traztuzumab | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: no |
| The HERA study team, 2005[48]<br><br>Month: May<br><br>Abstract (interim analysis)<br><br>Trial identifier: HERA (BIG 01–01) | $n = 5090$ enrolled<br><br>Intervention group 1: $n = 1694$, 1 year of trastuzumab<br><br>Intervention group 2: $n$ = not reported, 2 years of trastuzumab<br><br>Comparator: $n = 1693$, observation | Overall survival: at 2 years 96.0% (1 year of trastuzumab) vs 95.1% (observation); hazard ratio 0.76 (95% CI 0.47–1.23, $p = 0.26$). Events 29 (1 year of trastuzumab) vs 37 (observation)<br><br>Time to disease progression: DFS at 2 years 85.8% (1 year of trastuzumab) vs 77.4% (observation); hazard ratio 0.54 (95% CI 0.43–0.67, $p < 0.0001$). Events 127 (1 year of trastuzumab) vs 220 (observation)<br><br>2-year trastuzumab arm improved DFS compared with observation ($p < 0.0001$)<br><br>DFS at 2 years 89.7% (1 year of trastuzumab) vs 81.8% (observation); hazard ratio 0.51 (95% CI 0.40–0.66, $p < 0.0001$). Events 98 (1 year of trastuzumab) vs 179 (observation) | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: no |

***TABLE 13*** *Trastuzumab from STA: (early breast cancer)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| Smith, 2006[50]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: HERA | $n = 5102$ enrolled<br><br>Intervention group 1: $n = 1703$, 1 year of trastuzumab<br><br>Intervention group 2: 2 years of trastuzumab, not reported here<br><br>Comparator: $n = 1698$, observation | 2-year median follow-up time of 1 year of treatment – overall survival: hazard ratio 0.59 (95% CI 0.43–0.82, $p = 0.0016$); events 59 vs 90; 2 year 96.9% vs 93.6%<br><br>2-year median follow-up time of 1 year of treatment – disease progression: DFS hazard ratio 0.60 (95% CI 0.50–0.71, $p = 0.0001$); events 218 vs 321; 2 year 86.1% vs 78.0%<br><br>TTR: hazard ratio 0.57 (95% CI 0.48–0.69, $p = 0.0001$); events 198 vs 305; 2 year 87.3% vs 79.1%<br><br>TTDR: hazard ratio 0.56 (95% CI 0.46–0.68, $p = 0.0001$); events 160 vs 255; 2 year 90.1% vs 82.2% | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: yes |
| Smith *et al.*, 2007[51]<br><br>Month: January<br><br>Full publication<br><br>Trial identifier: HERA | Intervention: $n = 1703$, trastuzumab for 1 year<br><br>Comparator: $n = 1698$, observation alone | 2 year follow-up time of 1 year of treatment<br><br>Overall survival: 59 (3%) versus 90 (5%) deaths in the trastuzumab group and observation group respectively. The unadjusted hazard ratio for the risk of death in the trastuzumab group compared with the observation group was 0.66 (95% CI 0.47–0.91, $p = 0.0115$), which corresponds to an absolute overall survival benefit of 2.7% (92.4% vs 89.7%) at 3 years<br><br>Time to disease progression: 218 DFS events were reported with trastuzumab compared with 321 for observation. The unadjusted hazard ratio for the risk of an event in the trastuzumab group compared with the observation group was 0.64 (95% CI 0.54–0.76, $p < 0.0001$), which corresponds to an absolute DFS benefit of 6.3% (80.6% vs 74.3%) | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: yes |

*continued*

***TABLE 13*** *Trastuzumab: from STA (early breast cancer) (continued)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***BCIRG 006*** | | | |
| Slamon *et al.*, 2005[52]<br><br>Month: December<br><br>Abstract (first interim analysis)<br><br>Trial identifier: BCIRG 006 | Intervention: $n = 1073$, doxorubicin and cyclophosphamide plus docetaxel<br><br>Comparator 1: $n = 1074$, doxorubicin and cyclophosphamide plus docetaxel plus trastuzumab (AC-TH)<br><br>Comparator 2: $n = 1075$, docetaxel plus carboplatin plus trastuzumab (TCH) | Overall survival: not reported<br><br>Time to disease progression: DFS hazard ratio 0.49 with comparator 1 ($p = 0.00000048$) and 0.61 with comparator 2 ($p = 0.00015$) compared with intervention. No significant difference between the two trastuzumab-containing arms | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable).<br><br>Decision prior to this publication: no |
| Slamon 2007[53]<br><br>Month: April<br><br>Abstract (second interim analysis – taken from PP)<br><br>Trial identifier: BCIRG 006 | Intervention: $n = 1073$, doxorubicin and cyclophosphamide plus docetaxel (AC-T)<br><br>Comparator 1: $n = 1074$, doxorubicin and cyclophosphamide plus docetaxel plus trastuzumab (AC-TH)<br><br>Comparator 2: $n = 1075$, docetaxel plus carboplatin plus trastuzumab (TCH) | Overall survival at year 4: intervention 86%, comparator 2 91%, comparator 1 92%. Hazard ratio 0.59 (95% CI 0.42–0.85) with comparator 1 ($p = 0.004$) and 0.66 (95% CI 0.47–0.93) with comparator 2 ($p = 0.017$), compared with intervention<br><br>Time to disease progression: DFS hazard ratio 0.61 (95% CI 0.48–0.76) with comparator 1 ($p < 0.0001$) and 0.67 (95% CI 0.54–0.83) with comparator 2 ($p = 0.0003$) compared with intervention. Absolute DFS benefits (from year 2 to year 4): comparator 1 vs intervention 6%; comparator 2 vs intervention 5%<br><br>Disease free at year 4: intervention 77%, comparator 2 82%, comparator 1 83% | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: yes |

CI, confidence interval; DFS, disease-free survival; PP, PowerPoint presentation; TTDR, time to distant recurrence; TTR, time to recurrence.

***TABLE 14*** *Trastuzumab: new studies*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| Spielmann *et al.*, 2006[54]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: PACS 04 (clinical trial number: FRE-FNCLCC-PACS-04/0005) | First randomisation: intervention: $n = 1518$, 5-fluorouracil–epirubicin–cyclophosphamide (FEC100) vs $n = 1492$, epirubicin–docetaxel (ET75)<br><br>Followed by second randomisation of HER2-positive patients to two groups: $n = 259$ trastuzumab 1 year vs $n = 241$ observation only | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Results for toxicity and safety only for first randomisation | Date: August 2006<br><br>Decision: trastuzumab is recommended as a treatment option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)<br><br>Decision prior to this publication: yes |

## Gemcitabine (Gemzar®, Lilly)

***TABLE 15*** *Gemcitabine: from STA*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***JHQG*** | | | |
| O'Shaughnessy *et al.*, 2003[55]<br><br>Month: June<br><br>Abstract<br><br>Trial identifier: B9E-MC-JHQG, referred to as JHQG | Intervention: *n* = 267, gemcitabine plus paclitaxel (group 1)<br><br>Comparator: *n* = 262, paclitaxel alone (group 2) | Overall survival: reports insufficient events for overall survival, which will be determined at final analysis<br><br>Median time to disease progression: 5.4 months (95% CI 4.6–6.1) group 1 vs 3.5 months (95% CI 2.9–4.0) group 2 ($p = 0.0013$)<br><br>Hazard ratio 0.734 (95% CI 0.607–0.889, $p = 0.0015$) with an increased probability of approximately 50% for group 1 of being progression free at 6 months. PFS was significantly better with group 1 ($p = 0.0021$) | Date: Jan 2007<br><br>Decision: gemcitabine plus paclitaxel is recommended as a treatment option for women with metastatic breast cancer, but only in cases when docetaxel monotherapy or docetaxel plus capecitabine are also appropriate<br><br>Decision prior to this publication: no |
| Albain *et al.*, 2004[56]<br><br>Month: July<br><br>Abstract<br><br>Trial identifier: B9E-MC-JHQG, referred to as JHQG | Intervention: *n* = 267, gemcitabine plus paclitaxel (group 1)<br><br>Comparator: *n* = 262, paclitaxel alone (group 2) | Median overall survival: group 1 18.5 months (95% CI 16.5–21.2) vs group 2 15.8 months (95% CI 14.4–17.4). Hazard ratio 0.775 (95% CI 0.627–0.959) in favour of group 1 ($p = 0.018$). 1-year survival was group 1 70.7% (95% CI 65.1–76.3) versus group 2 60.9% (95% CI 54.8–66.9) ($p = 0.019$)<br><br>Time to disease progression: as reported above | Date: Jan 2007<br><br>Decision: gemcitabine plus paclitaxel is recommended as a treatment option for women with metastatic breast cancer, but only in cases when docetaxel monotherapy or docetaxel plus capecitabine are also appropriate<br><br>Decision prior to this publication: no |
| Moinpour *et al.*, 2004[57]<br><br>Month: July<br><br>Abstract<br><br>Trial identifier: B9E-MC-JHQG, referred to as JHQG | Intervention: *n* = 267, gemcitabine plus paclitaxel<br><br>Comparator: *n* = 262, paclitaxel alone | Overall survival: as reported in above<br><br>Time to disease progression: as reported in above<br><br>This abstract reports pain and QoL | Date: Jan 2007<br><br>Decision: gemcitabine plus paclitaxel is recommended as a treatment option for women with metastatic breast cancer, but only in cases when docetaxel monotherapy or docetaxel plus capecitabine are also appropriate<br><br>Decision prior to this publication: no |

CI, confidence interval; PFS, progression-free survival; QoL, quality of life.

***TABLE 16*** *Gemcitabine: from new searches*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***B9E-MC-S197*** | | | |
| Khoo *et al.*, 2004[58]<br><br>Month: July<br><br>Abstract<br><br>Trial identifier: B9E-MC-S197 | $n = 210$ enrolled, $n = 204$ for response assessment (breakdown in table not abstract)<br><br>Intervention 1: $n = 72$, gemcitabine 1250 mg/m$^2$ days 1 and 8 plus paclitaxel 175 mg/m$^2$ as 3-hour infusion day 1<br><br>Intervention 2: $n = 67$, gemcitabine 1000 mg/m$^2$ days 1 and 8 plus paclitaxel 100 mg/m$^2$ as 1-hour infusion days 1 and 8<br><br>Intervention 3: $n = 65$, gemcitabine 1000 mg/m$^2$ days 1 and 8 plus docetaxel 40 mg/m$^2$ as 1-hour infusion days 1 and 8 | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Efficacy outcomes were similar in the three arms – no data reported. Results for toxicity, side-effects and adverse events | Date: Jan 2007<br><br>Decision: gemcitabine plus paclitaxel is recommended as a treatment option for women with metastatic breast cancer, but only in cases when docetaxel monotherapy or docetaxel plus capecitabine are also appropriate<br><br>Decision prior to this publication: no |
| Khoo *et al.*, 2006[59]<br><br>Month: August<br><br>Full publication<br><br>Trial identifier: B9E-MC-S197 | $n = 210$ randomised, $n = 204$ for response assessment<br><br>Intervention 1: $n = 73$ (72) group 1, gemcitabine 1250 mg/m$^2$ days 1 and 8 plus paclitaxel 175 mg/m$^2$ as 3-hour infusion day 1<br><br>Intervention 2: $n = 69$ (67) group 2, gemcitabine 1000 mg/m$^2$ days 1 and 8 plus paclitaxel 100 mg/m$^2$ as 1-hour infusion days 1 and 8<br><br>Comparator: $n = 68$ (65) group 3, gemcitabine 1000 mg/m$^2$ days 1 and 8 plus docetaxel 40 mg/m$^2$ as 1-hour infusion days 1 and 8 | Overall survival: not reported<br><br>Time to disease progression: group1 7.5 months, group 2 7.0 months, group 3 7.4 months<br><br>Hazard ratio estimate (95% CI): group 1 vs group 2, 0.96 (0.65–1.42); group 1 vs group 3, 0.97 (0.65–1.44); group 2 vs group 3, 1.01 (0.68–1.51) | Date: Jan 2007<br><br>Decision: gemcitabine plus paclitaxel is recommended as a treatment option for women with metastatic breast cancer, but only in cases when docetaxel monotherapy or docetaxel plus capecitabine are also appropriate<br><br>Decision prior to this publication: no |

CI, confidence interval.

## Lapatinib (Tykerb®, GlaxoSmithKline)

***TABLE 17*** *Lapatinib: no previous NICE guidance*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***NCT00078572*** | | | |
| Geyer *et al.*, 2006[60]<br><br>Month: December<br><br>Full publication (interim analysis – early reporting on the basis of superiority of combination treatment)<br><br>Trial identifier: clinical trial number: NCT00078572 | Intervention: $n = 163$, lapatinib plus capecitabine<br><br>Comparator: $n = 161$, capecitabine | Overall survival: not reported per se but 22% deaths for dual therapy and 22% deaths for monotherapy; hazard ratio 0.92 (95% CI 0.58–1.46, $p = 0.72$)<br><br>Median time to disease progression: 8.4 months, 49 disease progression events (dual therapy) vs 4.4 months, 72 events (monotherapy); hazard ratio 0.49 (95% CI 0.34–0.71, $p < 0.001$) | Date: NA<br><br>Decision: none<br><br>Decision prior to this publication: no |
| Geyer *et al.*, 2007[61]<br><br>Month: June<br><br>Abstract (updated efficacy analysis and interim correlative analysis of gene expression levels)<br><br>Trial identifier: EGF100151 | Intervention: lapatinib plus capecitabine (group 1)<br><br>Comparator: capecitabine (group 2)<br><br>Data available for $n = 217/399$ so far | Overall survival: group 1 vs group 2 hazard ratio 0.78 (95% CI 0.55–1.12, $p = 0.177$)<br><br>Time to disease progression:<br><br>TTP: group 1 27 weeks vs group 2 19 weeks; hazard ratio 0.57 (95% CI 0.43–0.77, $p = 0.00013$)<br><br>ORR: group 1 24% vs group 2 14%; odds ratio 1.90 (95% CI 1.00–1.34, $p = 0.017$)<br><br>Progression in CNS metastases: group 1 2% vs group 2 11% ($p = 0.0445$) | Date: NA<br><br>Decision: none<br><br>Decision prior to this publication: no |
| ***Sherrill*** | | | |
| Sherrill *et al.*, 2007[62]<br><br>Month: June<br><br>Abstract | Intervention: $n = 198$ (ITT), lapatinib plus capecitabine (group 1)<br><br>Comparator: $n = 201$ (ITT), capecitabine (group 2) | Overall median survival: 67 weeks (based on 2006 data); 7 weeks' difference in quality-adjusted survival favouring group 1 (p=0.0013).Time to disease progression: not reported | Date: NA<br><br>Decision: none<br><br>Decision prior to this publication: no |

*continued*

***TABLE 17*** *Lapatinib: no previous NICE guidance (continued)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***Cameron*** | | | |
| Cameron *et al.*, 2006[63]<br><br>Month: December<br><br>Abstract (interim analysis) | Intervention: lapatinib plus capecitabine (group 1)<br><br>Comparator: capecitabine alone (group 2)<br><br>*n* = 321 to date, randomised 1:1 – no breakdown | Overall survival: not reported<br><br>Median PFS: group 1 36.9 weeks vs group 2 17.9 weeks; hazard ratio 0.48 (95% CI 0.33–0.70, log-rank *p* = 0.000045)<br><br>Median time to disease progression: group 1 36.9 weeks vs group 2 19.7 weeks; hazard ratio 0.51 (95% CI 0.35–0.74, log-rank *p* = 0.00016) | Date: NA<br><br>Decision: none<br><br>Decision prior to this publication: no |

CI, confidence interval; CNS, central nervous system; ITT, intention to treat; NA, not applicable; ORR, overall response rate; PFS, progression-free survival; TTP, time to progression.

## Bevacizumab (Avastin®, Roche)

***TABLE 18*** *Bevacizumab: no previous NICE guidance*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| ***Miller*** | | | |
| Miller *et al.*, 2005[65]<br>Month: February<br>Full publication | Intervention: *n* = 232, capecitabine with bevacizumab (group 1)<br>Comparator: *n* = 230, capecitabine (group 2) | Median overall survival: 15.1 months group 1 vs 14.5 months group 2 – comparable in both treatment groups<br>Time to disease progression: median PFS: 4.86 months group 1 vs 4.17 months group 2; hazard ratio 0.98 | No NICE guidance at present<br>Decision prior to this publication: no |
| Miller *et al.*, 2002[64]<br>Month: December<br>Abstract | Intervention: capecitabine with bevacizumab (group 1)<br>Comparator: capecitabine (group 2)<br>*n* = 462 randomised, no breakdown | Overall survival: not reported<br>Time to disease progression: not reported<br>Results on baseline data only. Full analysis due September 2002 | No NICE guidance at present<br>Decision prior to this publication: no |
| ***Overmoyer*** | | | |
| Overmoyer *et al.*, 2004[67]<br>Month: December<br>Abstract | Intervention: *n* = 20, bevacizumab and docetaxel (group 1)<br>Comparator: *n* = 18, docetaxel (group 2) | Overall survival: not reported<br>Time to disease progression: not reported<br>Results on tumour size, toxicity, IAUC and serum VCAM-1 levels | No NICE guidance at present<br>Decision prior to this publication: no |
| Overmoyer *et al.*, 2004[66]<br>Month: July<br>Abstract | Intervention: bevacizumab and docetaxel (group 1)<br>Comparator: docetaxel (group 2)<br>*n* = 33 randomised to date, no breakdown | Overall survival: not reported<br>Time to disease progression: not reported<br>Results on tumour size and toxicity | No NICE guidance at present<br>Decision prior to this publication: no |
| ***E2100*** | | | |
| Miller *et al.*, 2005[68]<br>Month: December<br>Abstract<br>Trial identifier: E2100 (Eastern Cooperative Oncology Group, ECOG) | Intervention: paclitaxel with bevacizumab (group 1)<br>Comparator: paclitaxel (group 2)<br>*n* = 722 enrolled, no breakdown | Overall survival: data are immature – early follow-up suggests that group 1 has improved overall survival (hazard ratio 0.674, $p = 0.01$)<br>Time to disease progression: group 1 has significantly prolonged PFS (10.97 months vs 6.11 months; hazard ratio 0.498, $p < 0.001$)<br>Group 1 significantly increased response rates in all patients (28.2% vs 14.2%; $p < 0.0001$) and in the subset of patients with measurable disease (34.3% vs 16.4%; $p < 0.0001$) | No NICE guidance at present<br>Decision prior to this publication: no |

*continued*

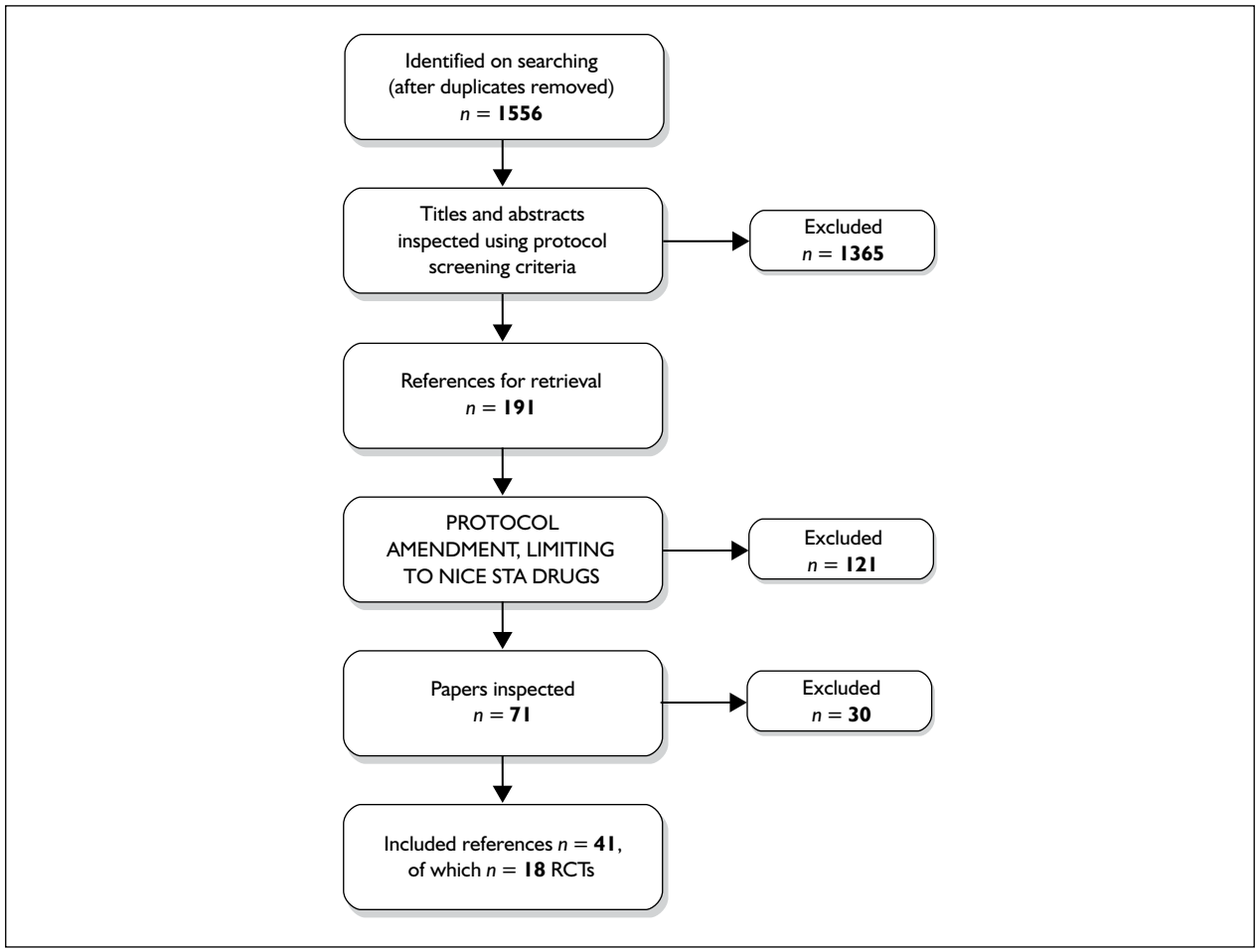
***TABLE 18*** *Bevacizumab: no previous NICE guidance (continued)*

| Publication details | Number of participants | Key outcomes | Decisions by NICE |
|---|---|---|---|
| Wagner *et al.*, 2006[69]<br><br>Month: December<br><br>Abstract<br><br>Trial identifier: Eastern Co-operative Oncology Group (ECOG) study E2100<br><br>Lyons | Intervention: *n* = 368, paclitaxel with bevacizumab (group 1)<br><br>Comparator: *n* = 354, paclitaxel (group 2) | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Results on self-reported symptom burden and HRQoL – improvement in clinical outcomes stated but data not reported | No NICE guidance at present<br><br>Decision prior to this publication: no |
| Lyons *et al.*, 2006[70]<br><br>Month: June<br><br>Abstract | Intervention: *n* = 24, bevacizumab and docetaxel (group 1)<br><br>Comparator: *n* = 25, docetaxel (group 2) | Overall survival: not reported<br><br>Time to disease progression: not reported<br><br>Phase II study – results on tumour size, toxicity, wound healing and changes in LVEF | No NICE guidance at present<br><br>Decision prior to this publication: no |
| ***Burstein*** | | | |
| Burstein *et al.*, 2005[71]<br><br>Month: December<br><br>Abstract (interim analysis) | Intervention: (*n* = 34) cyclophosphamide and methotrexate plus bevacizumab<br><br>Comparator: (*n* = 21) cyclophosphamide and methotrexate<br><br>(Information in parentheses from internet)<br><br>At the time of this publication, *n* = 41 enrolled with accrual of a further 13 to dual therapy continuing | Overall survival: not reported<br><br>Time to disease progression: not reported | No NICE guidance at present<br><br>Decision prior to this publication: no |

HRQoL, health-related quality of life; IAUC, incremental area under the curve; LVEF, left ventricular ejection fraction; PS, progression-free survival; VCAM-1, vascular cell adhesion molecule-1.

# Appendix 3

## Flow chart of systematic review process



# Appendix 4

## Details of related ongoing trials

### Paclitaxel

NCT00041119. A trial comparing cyclophosphamide and doxorubicin (CA) (four versus six cycles) versus paclitaxel (four versus six cycles) as adjuvant therapy for breast cancer in women with 0–3 positive auxiliary lymph nodes. Study type: 2 ×2 factorial phase III RCT. Sample size: 4646. Start date: May 2002. End date: not reported. Status: currently recruiting patients. Funding: Cancer and Leukemia Group B, National Cancer Institute. Funding amount: not reported.

### Lapatinib

N0051189183. This trial is an open-label expanded access study of lapatinib and capecitabine therapy in women with HER2 (ErbB2) overexpressing locally advanced or metastatic breast cancer. Study type: multicentre, single-arm, open-label, expanded access study. Sample size: approximately eight. Start date: September 2006. End date: not reported [the study will continue to run and enrol subjects until the Medicines and Healthcare Products Regulatory Agency (MHRA) gives approval for lapatinib]. Status: ongoing. Funding: GlaxoSmithKline. Funding amount: not reported.

N0258184664/NCT00347919. A phase II, open-label, randomised, multicentre trial of GW786034 (pazopanib) in combination with lapatinib (GW572016) compared with lapatinib alone as first-line therapy in women with advanced or metastatic breast cancer with ErbB2 fluorescence in situ hybridisation (FISH)-positive tumours. Study type: open-label, multicentre, phase II safety/efficacy RCT. Sample size: 140. Start date: June 2006. End date: not reported. Status: currently recruiting patients. Funding: GlaxoSmithKline. Funding amount: not reported.

### Docetaxel

NCT00408408. A randomised phase III trial of neoadjuvant therapy in patients with palpable and operable breast cancer, evaluating the effect on the pathological complete response (pCR) of adding capecitabine or gemcitabine to docetaxel when administered before adjuvant chemotherapy (AC) with or without bevacizumab. Study type: phase III RCT. Sample size: 1200. Start date: November 2006. End date: not reported. Status: currently recruiting patients. Funding: National Surgical Adjuvant Breast and Bowel Project (NSABP), National Cancer Institute. Funding amount: not reported.

NCT00391092. A randomised open-label study to compare the effect of first-line treatment with Avastin in combination with Herceptin/docetaxel with Herceptin/docetaxel alone on progression-free survival in patients with HER2-positive locally recurrent or metastatic breast cancer. Study type: open-label, phase III, safety/efficacy RCT. Sample size: target 100–500. Start date: September 2006. End date: not reported. Status: currently recruiting patients. Funding: Hoffmann-La Roche. Funding amount: not reported.

### Bevacizumab

NCT00262067. A multicentre, phase III, randomised, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in women with previously untreated metastatic breast cancer. Study type: phase III multicentre RCT. Sample size: 1200. Start date: December 2005. End date: not reported. Status: currently recruiting patients. Funding: Genentech, Hoffmann-La Roche. Funding amount: not reported.

NCT00281697. A phase III, multicentre, randomised, placebo-controlled trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy regimens in women with previously treated metastatic breast cancer. Study type: phase III multicentre RCT. Sample size: 700. Start date: February 2006. End date: not reported. Status: currently recruiting patients. Funding: Genentech. Funding amount: not reported.

NCT00433511. A double-blind phase III trial of doxorubicin hydrochloride liposome and cyclophosphamide followed by paclitaxel with bevacizumab or placebo in patients with lymph node-positive and high-risk lymph node-negative breast cancer. Study type: phase III, open-label, multicentre RCT. Sample size: 4950. Start date:

January 2006. End date: not reported. Status: not yet open for patient recruitment. Funding: Eastern Cooperative Oncology Group, National Cancer Institute (NCI), North Central Cancer Treatment Group, Cancer and Leukemia Group B. Funding amount: not reported.

NCT00373256. A phase III study of SU011248 in combination with paclitaxel versus bevacizumab with paclitaxel in the first-line advanced disease setting in patients having breast cancer. Study type: phase III open-label RCT. Sample size: 740. Start date: November 2006. End date: not reported. Status: currently recruiting patients. Funding: Pfizer. Funding amount: not reported.

## Trastuzumab

MREC reference MREC01/1/68 (N0258107389, N0265110588, N0143108959 N0205108841). The HERA trial is a phase III multicentre RCT with three arms, comparing 1 and 2 years of Herceptin with no Herceptin in women with HER2-positive primary breast cancer who have completed adjuvant chemotherapy. Sample size: 3192. Start date: 1 November 2001. End date: 31 January 2015. Status: project ongoing. Some funding is provided by Roche, as well as NIHR (N0265110588 only). Funding amount: only reported for N0265110588: £140,000 Roche, NIHR £12,500.24.

NCT00381901 (study ID numbers: CDR0000509793; INCA-PHARE; INCA-RECF0146; EUDRACT-2006–000070–67). A randomised phase III trial comparing 6 or 12 months of adjuvant trastuzumab treatment in women with non-metastatic breast cancer that can be removed by surgery, stratified according to participating centre, modality of adjuvant chemotherapy (concurrent versus sequential), and adjuvant hormonal therapy (yes versus no), with a 5-year follow-up. Study design: phase III, treatment, randomised, active control. Sample size: 7000. Start date: May 2006. End date: not reported. Status: currently recruiting. Funding provided by the National Cancer Institute, France. Funding amount: not reported.

## Adjuvant lapatinib and/ or trastuzumab

NCT00490139 (study ID numbers: EGF106708; BIG 2–06/N063D); ALTTO: A trial comparing lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with HER2/ErbB2-positive primary breast cancer. Study design: phase III, treatment, randomised, open-label, active control, parallel assignment, safety/efficacy study (Breast International Group, North Central Cancer Treatment Group). Sample size: 8000. Start date: May 2007. End date: not reported. Status: currently recruiting in some countries. Funded by GlaxoSmithKline. Funding amount: not reported.

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***We look forward to hearing from you.***

The NIHR Coordinating Centre for Health Technology Assessment
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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