

A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab for breast cancer

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CONTENTS

EXECUTIVE SUMMARY	6
LIST OF ABBREVIATIONS	9
DEFINITIONS OF TERMS	10
1. AIM OF THE REVIEW	14
2. BACKGROUND	14
2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM	14
2.2 CURRENT SERVICE PROVISION	15
2.3 DESCRIPTION OF TECHNOLOGY	15
3. EFFECTIVENESS AND COST-EFFECTIVENESS	18
3.1 METHODS OF THE REVIEW	18
3.2 EFFECTIVENESS	22
QUANTITY AND QUALITY OF RESEARCH AVAILABLE	22
ASSESSMENT OF EFFECTIVENESS	34
3.3 ECONOMIC ANALYSIS	52
QUANTITY AND QUALITY OF ECONOMIC EVALUATIONS	52
ASSESSMENT OF COST-EFFECTIVENESS	58
4. DISCUSSION	60
4.1 MAIN RESULTS	60
4.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES	62
4.3 NEED FOR FURTHER RESEARCH	65
5. CONCLUSIONS	66
6. REFERENCES	67

LIST OF APPENDICES

Appendix 1.	Literature searches
Appendix 2.	Excluded studies.
Appendix 3.	Staging of breast cancer
Appendix 4.	Quality checklists
Appendix 5.	Levels of evidence based on those developed by members of the NHS R&D Centre for Evidence-Based Medicine
Appendix 6.	Trastuzumab combination therapy trial
Appendix 7.	Trastuzumab monotherapy studies included in the update
Appendix 8.	Ongoing trastuzumab trials
Appendix 9.	Economic evaluation for trastuzumab
Appendix 10.	Industry submission data presented to NICE

LIST OF TABLES

Table 1:	The evidence base for trastuzumab
Table 2:	Trastuzumab – summary of included studies
Table 3:	Quality of the included trastuzumab combination therapy trial
Table 4:	Quality of the included trastuzumab monotherapy studies
Table 5:	Quality of the included trastuzumab monotherapy therapy trial
Table 6:	Summary of tumour response for trastuzumab plus chemotherapy
Table 7:	Summary of tumour response for trastuzumab plus paclitaxel
Table 8:	Summary of duration of response (months) for trastuzumab plus chemotherapy
Table 9:	Summary of duration of response (months) for trastuzumab plus paclitaxel
Table 10:	Summary of survival (months) for trastuzumab plus chemotherapy
Table 11:	Summary of mortality rates at 1 year for trastuzumab plus chemotherapy
Table 12:	Summary of patient deaths for trastuzumab plus chemotherapy
Table 13:	Summary of survival (months) for trastuzumab plus paclitaxel
Table 14:	Summary of mortality rates at 1 year for trastuzumab plus paclitaxel
Table 15:	Severe adverse events (that occurred in more than 10 percent of participants) for trastuzumab plus chemotherapy
Table 16:	Severe adverse events (that occurred in more than 10 percent of participants) for trastuzumab plus paclitaxel
Table 17:	Commerical in confidence data removed
Table 18:	Overview of cardiac events incidence
Table 19:	Quality of life for trastuzumab plus chemotherapy
Table 20:	Summary of tumour response for trastuzumab monotherapy
Table 21:	Summary of stable and progressive disease for trastuzumab plus paclitaxel monotherapy
Table 22:	Summary of duration of response (months) for trastuzumab monotherapy
Table 23:	Summary of survival (months) for trastuzumab monotherapy
Table 24:	Severe adverse events (grade 3 or 4) for trastuzumab monotherapy
Table 25:	Overview of the incidence of CREC diagnosed cardiac events for trastuzumab monotherapy
Table 26:	Summary of the trastuzumab combination therapy findings
Table 27:	Summary of the trastuzumab monotherapy findings
Table 28:	Quality checklist for economic evaluations of trastuzumab

LIST OF FIGURES

Figure 1:	Incremental cost of intervention compared to control
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EXECUTIVE SUMMARY

Trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) is a recombinant humanised monoclonal antibody that specifically targets the HER2 protein. It is used in patients with metastatic breast cancer (MBC) who have tumours that overexpress HER2.

Background

Breast cancer is the leading cause of cancer deaths amongst women in the UK. Figures suggest that between 16-20% of women initially presenting with breast cancer have advanced disease with distant metastases and around 50% of patients presenting with early or localised breast cancer will eventually progress to develop advanced or metastatic disease.

The prognosis of MBC depends on age, extent of disease, oestrogen receptor status, and previous chemotherapy treatment. There is also evidence that the overexpression of the product of the epidermal growth factor receptor 2 (HER2) oncogene is an important prognostic factor, indicating a more aggressive form of the disease, with a more rapid progression and shortened survival time.

MBC is considered to be incurable and treatment is usually focused on relieving symptoms and improving the quality of life with as little treatment-related toxicity as possible. Trastuzumab is a relatively new anti-cancer agent that may be beneficial in a specific group of patients who are identified as having tumours that strongly overexpress HER2.

Methods

The following databases were searched using strategies designed specifically for each database: MEDLINE, EMBASE, Cancerlit, BIOSIS, Index to Scientific and Technical Proceedings, Cochrane Controlled Trials Register (CCTR), National Research Register (NRR), Database of Abstracts and Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NHSEED). Additional references were identified through reviewing manufacturer and sponsor submissions made to the National Institute for Clinical Excellence (NICE), the bibliographies of retrieved articles, conference proceedings and by searching the Internet.

Only randomised controlled trials (RCTs) and full economic evaluations were initially considered for inclusion. Included trials had to evaluate trastuzumab alone or in combination with other agents versus systemic therapy without trastuzumab. Only trials that included individuals with breast cancer were included.

No RCTs of trastuzumab used as monotherapy for the treatment of breast cancer were found. NICE therefore requested that non-comparative phase II studies of trastuzumab used as monotherapy for the treatment of HER2 overexpressing (at level 3+) breast cancer be evaluated for inclusion in the review. This data has subsequently been added to this review.

Data was extracted by one reviewer and checked by a second reviewer. Quality assessment was conducted independently by two reviewers. Disagreements were resolved by consensus and when necessary by recourse to a third reviewer. The primary outcomes of interest were response, quality of life, time to disease progression, overall survival, relief of symptoms and cost. Results of data extraction and quality assessment were presented in structured tables and also as a narrative

summary. Studies were grouped according to the type intervention (monotherapy or combination therapy).

Results

Effectiveness data

Combination therapy

There was only one included RCT of trastuzumab plus chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone. The study population included women with overexpressing HER2 MBC at level 2+ or 3+ who had not received prior treatment for MBC. The overall quality of the included trial was considered to be good. Trastuzumab was administered for the duration of the trial in weekly infusions as long as the treatment was considered to be beneficial.

The addition of trastuzumab to chemotherapy resulted in significantly less disease progression and treatment failure and greater overall response when compared to chemotherapy alone. However, there was no significant difference between the two treatment groups for complete response. Participants treated with trastuzumab plus chemotherapy had significantly longer progression free survival than those treated with chemotherapy alone. There was a significantly greater incidence of congestive heart failure reported among those treated with trastuzumab plus chemotherapy compared to those on chemotherapy alone. The incidence seemed to be highest amongst those treated with trastuzumab plus anthracycline (approximately a quarter of the participants), rather than those who received trastuzumab plus paclitaxel.

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Monotherapy

There were no RCTs found that met the initial inclusion criteria therefore, this section is based on non-comparative phase II studies. The overall quality of these studies according to the checklist for case series was found to be moderate. Trastuzumab monotherapy was shown to have some antitumour effects in terms of overall response (partial and complete) which according to three studies ranged from 12% to 24%. An independent response committee assessed response outcomes in two studies whereas response was assessed by the investigators in the third study (H0650g). Similar duration of response was reported by two studies ranging from 9 months (study H0650g) to 9.1 months (study H0649g).

Only one study (H0649g) reported the number of complete or partial responses for participants with tumours overexpressing HER2 at level 3+, which included 5 (3%) complete and 26 (15%) partial responses. For study H0650g, the overall response rate for this group of participants was reported for both treatment groups combined and included 31% (26/85). These results showed that the majority of tumour responses appeared in participants with tumours overexpressing HER2 at level 3+.

Two studies reported data on survival end points (H0649g and H0650g). One study (H0649g) reported that the overall median survival time using Kaplan-Meier methodology was 13 months (range 0.5 to 30), and that for participants with tumours overexpressing HER2 at level 3+ it was 16.4 months. The median follow-up for this study was 12.8 months. For the second study (H0650g), 67% of participants were reported to be alive at a median follow-up of 11 months, with survival duration ranging from 1.2 to 35.3 months.

Trastuzumab when used as a single agent appears to have a relatively low toxicity level.

Economic data

The industry submission data included two economic evaluations. One evaluated trastuzumab as combination therapy with paclitaxel versus paclitaxel alone and one evaluated trastuzumab as monotherapy versus vinorelbine. Several important elements relating to the methods of both economic evaluations were classified as confidential.

The economic evaluation of trastuzumab as combination therapy (for first line therapy for MBC) was relatively well conducted. The incremental cost per LYG for trastuzumab in combination with paclitaxel was £14,069 and the cost per QALY was £29,448. However, it is important to note that the data on survival was extrapolated from survival curves that only included participants who did not switch to trastuzumab on disease progression, all of whom had very poor prognosis and died during the trial.

The economic evaluation of trastuzumab as monotherapy was not considered to be as good and the cost analysis was of limited validity as was the effectiveness evidence it is based on. The incremental cost per LYG for trastuzumab was £7,521. This ratio was driven by an assumed significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

Conclusions

TRASTUZUMAB

Trastuzumab when used in combination with chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) seems to be more effective than chemotherapy alone for the treatment of MBC over expressing HER2 at level 3+ in individuals who have not received prior treatment for MBC. However, it seems to be associated with congestive heart failure particularly in patients receiving anthracycline based chemotherapy. **Commercial in confidence information removed.**

When compared to paclitaxel, trastuzumab used in combination therapy with paclitaxel for first line therapy for MBC was found to have a matrix score of A (higher costs but better outcomes) and an incremental cost effectiveness ratio of £14,069 LYG and £29,448 per QALY.

Trastuzumab monotherapy when used as second line or subsequent therapy for the treatment of MBC overexpressing HER2 at level 3+ appears to have some antitumour effects in terms of overall response (partial and complete) based on non-comparative studies (which constitutes weak evidence) of moderate quality. No included study compared the use of trastuzumab with an alternative systemic therapy and the findings may therefore be subject to bias. Without better effectiveness data, it is difficult to adequately assess the cost effectiveness of trastuzumab monotherapy.

When compared to vinorelbine, trastuzumab monotherapy for second line therapy for MBC was found to have a matrix score of A and an incremental cost effectiveness ratio of £7,521 per LYG. However, this ratio was driven by an assumed significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

Implications for further research

Further large well-conducted RCTs are required to investigate the effectiveness of trastuzumab within the settings for which it is currently indicated.

LIST OF ABBREVIATIONS

ABC	Advanced Breast Cancer
BNF	British National Formulary
CBA	Cost benefit analysis
CCA	Cost consequence analysis
CEA	Cost effectiveness analysis
CER	Cost-effectiveness Ratio
CI	Confidence Interval
CMA	Cost minimisation analysis
CUA	Cost utility analysis
CMF	The combination of cyclophosphamide, methotrexate and 5-fluorouracil
CR	Complete response
CREC	Cardiac review and evaluation committee
DRG	Diagnosis Related Group
EORTC	European Organization for Research and Treatment of Cancer
HER2	Human epidermal growth factor receptor 2
HRG	Health Related Group
HRQL	Health related quality of life
IHC	Immunohistochemistry
ITT	Intention to treat (analysis)
KPS	Karnofsky performance scale
LYG	Life Years Gained
MBC	Metastatic breast cancer
MD	Mean difference
OR	Overall or objective response
PFLYG	Progression-free Life Years Gained
PR	Partial response
QOL	Quality of Life
QALY	Quality Adjusted Life Years
RCT	Randomised controlled trial
REC	Response evaluation committee
RR	Relative risk
UKCCCR	United Kingdom Co-ordinating Committee on Cancer Research. The national committee responsible for co-ordinating clinical trials for cancer treatment in the UK.
WHO	World Health Organisation

DEFINITIONS OF TERMS

Absolute risk reduction The decreased chance of having an outcome from the treatment compared to the comparator, or the increased chance of not having an outcome from the comparator compared to the treatment. In oncology, this can be considered as e.g. the reduction of the risk of not responding to treatment.

Adjuvant treatment This usually refers to systemic chemotherapy or hormonal treatment or both, taken by patients after removal of a primary tumour (in this case, surgery for early breast cancer), with the aim of killing any remaining micrometastatic tumour cells and thus preventing recurrence.¹

Advanced disease Locally advanced (stage III) and metastatic (stage IV) disease (see also Appendix 3, Staging of breast cancer).

Anthracycline refractory Never responded to anthracycline therapy.

Anthracycline resistance The development of resistance to anthracyclines after initial response to first line treatment with combinations containing anthracycline.

Arthralgia Pain in the joints or in a single joint.

Ascites An accumulation of fluid in the abdominal (peritoneal) cavity.

Carcinoma A cancerous growth.

Chemotherapy The use of drugs that kill cancer cells, or prevent or slow their growth.

Clinical Oncologist A doctor who specialises in the treatment of cancer patients, particularly through the use of *radiotherapy*, but who may also use *chemotherapy*.

Combination chemotherapy regimens The use of more than one drug to kill cancer cells.

Classical CMF Cyclophosphamide (100mg/m² orally days 1-14), methotrexate (40mg/m² intravenously (iv) day 1 + 8), and 5-fluorouracil (600mg/m² iv day 1 + 8), every 4 weeks for up to six cycles of treatment given dependent on response.

CAF Cyclophosphamide (500mg/m² iv), doxorubicin (50mg/m²iv), and 5-fluorouracil (500mg/m² iv), every 3 weeks for up to six cycles of treatment given dependent on response.

FEC 5-fluorouracil, epirubicin, and cyclophosphamide every 3 weeks for up to six cycles of treatment given dependency on response.

FAC 5-fluorouracil, doxorubicin, and cyclophosphamide every 3 weeks for up to six cycles of treatment given dependency on response.

Complete response Total disappearance of all detectable malignant disease for at least 4 weeks (must state measurement device/ technology).

Cost-utility analysis Analysis in which the additional cost per quality adjusted life year (QALY) saved or gained is estimated.

Cycle Chemotherapy is usually administered at regular (normally monthly) intervals. A cycle is a course of chemotherapy followed by a period in which the patient's body recovers.

Cytology The study of the appearance of individual cells under a microscope.

Cytotoxic Toxic to cells. This term is used to describe drugs which kill cancer cells or slow their growth.

Debulking Removal by surgery of a substantial proportion of cancer tissue. Optimal debulking refers to the removal of the largest possible amount of cancer while limiting damage to normal tissue; interval debulking refers to surgical removal of tumour after *chemotherapy* aimed at further reducing its bulk.

Differentiation The degree of morphological resemblance between cancer tissue and the tissue from which the cancer developed.

Disease free interval Time between surgery for early breast cancer and developing metastatic breast cancer.

Early breast cancer Operable disease (stage I or II), restricted to the breast and sometimes to local lymph nodes.

First line treatment Initial treatment for a particular condition that has previously not been treated. For example, first line treatment for metastatic breast cancer may include chemotherapy or hormonal therapy, or both.¹). Used in advanced disease where the treatment intent may be curative (e.g. in some cases of locally advanced disease) but is usually palliative. The main treatment modality is systemic therapy.

Heterogeneous Of differing origins, or different types.

Histological grade Degree of malignancy of a tumour, usually judged from its histological features.

Histological type The type of tissue found in a tumour.

Histology An examination of the cellular characteristics of a tissue.

Incremental cost effectiveness analysis Estimates of the additional cost per specific clinical outcome.

Locally advanced disease (breast) Disease which has infiltrated the skin or chest wall or disease which has involved axillary nodes.

Localised disease Tumour confined to a small part of an organ.

Lymph nodes Small organs which act as filters in the lymphatic system. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads.

Marginal or minor response Less than 50% but greater than 25% tumour regression for all measurable tumours for at least 4 weeks with no new lesions appearing (measurement technique must be stated).

Measurable lesion Lesion which could be unidimensionally or bidimensionally measured by physical examination, echography, x-rays or CT scan.

Medical Oncologist Doctor who specialises in the treatment of cancer through the use of *chemotherapy*.

Meta-analysis The statistical analysis of the results of a collection of individual studies to synthesise their findings.

Metastasis Spread of cancer cells from the original site to other parts of the body via the blood circulation or lymphatic system.

Metastatic breast cancer Stage IV breast cancer (see also Appendix 3, Staging of breast cancer).

Myalgia Muscle pain.

Neo-adjuvant treatment Treatment given before the main treatment; usually *chemotherapy* or *radiotherapy* given before surgery.

Non-measurable lesion No exact measurements could be obtained e.g. pleural effusions, ascites.

Objective or Overall response A complete or *partial response*.

Oestrogen receptor (ER) A protein on breast cancer cells that binds oestrogens. It indicates that the tumour may respond to hormonal therapies. Patients with tumours rich in oestrogen receptors have a better prognosis than those with tumours which are not.

Palliative Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it. Hence palliative care, palliative *chemotherapy*.

Partial response At least 50% decrease in tumour size for >4 weeks without an increase in the size of any area of known malignant disease or the appearance of new lesions (definitions vary between trials – technique used for measurement must be stated).

Primary anthracycline resistance Failure to respond to a first or second line anthracycline (disease progression) or relapse.

Progressive disease The tumour continues to grow or the patient develops more metastatic sites.

Prophylaxis An intervention used to prevent an unwanted outcome.

Protocol A policy or strategy which defines appropriate action.

Quality Adjusted Life Years Index of survival that is weighted or adjusted by the patient's quality of life during the survival period.

Quality of Life The individual's overall appraisal of her situation and subjective sense of well-being.

Radiotherapy The use of radiation, usually X-rays or gamma rays, to kill tumour cells.

Recurrence/disease free survival The time from the primary treatment of the breast cancer to the first evidence of cancer recurrence.

Refractory disease: Disease that has never responded to first line therapy.

Remission A period when cancer has responded to treatment and there are no signs of tumour or tumour-related symptoms.

Secondary anthracycline resistance Disease progression after initial objective response to first or second line therapy or disease progression during treatment with an anthracycline.

Salvage therapy Any therapy given in the hope of getting a response when the "standard" therapy has failed. This may overlap with "second-line" therapy, but could also include therapy given for patients with refractory disease i.e. disease that has never responded to first-line therapy.

Second-line therapy The second chemotherapy regimen administered either as a result of relapse after first-line therapy or immediately following on from first-line therapy in patients with progressive or stable disease. Depending on the circumstances patients may be treated with the same regimen again, or a different regimen. In either case this is defined as second-line therapy.

Stable disease No change or less than 25% change in measurable lesions for at least 4 to 8 weeks with no new lesions appearing.

Staging The allocation of categories (stage I to IV) to tumours defined by internationally agreed criteria. Stage I tumours are localised, whilst stage II to IV refer to increasing degrees of spread through the body from the primary site. Tumour stage is an important determinant of treatment and prognosis.

Time to progression The length of time from the start of treatment (or time from randomisation within the context of a clinical trial) until tumour progression.

Utility approach Assigns numerical values on a scale from 0 (death) to 1 (optimal health). It provides a single number that summarises all of health related quality of life – a global measure of health related life quality.

Utility scores Strength of a patient's preference for a given health state or outcome.

Utilities A measure of value of an outcome that reflects attitude towards the probability of that outcome occurring.

Values Preferences without risk or uncertainty.

1. AIM OF THE REVIEW

The objectives of the review were to evaluate the clinical effectiveness and cost-effectiveness of trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) in the management of advanced breast cancer. Only randomised controlled trials of trastuzumab alone, or in combination with other agents, versus systemic therapy without trastuzumab, were initially considered in the assessment of clinical effectiveness. The assessment of cost effectiveness includes only full economic evaluations.

No RCTs of trastuzumab used as monotherapy for the treatment of breast cancer were found. The National Institute for Clinical Excellence (NICE) therefore requested that non-comparative phase II studies of trastuzumab used as monotherapy for the treatment of HER2 overexpressing (at level 3+) breast cancer be evaluated for inclusion in the review. This data has subsequently been added to this review. Only participants who had either been pre-treated with an anthracycline and/or a taxane or for whom these treatments were unsuitable were included in this update.

2. BACKGROUND

2.1 DESCRIPTION OF UNDERLYING HEALTH PROBLEM

Breast cancer is the leading cause of death amongst women aged 35 to 54 in the UK.² It is the most common cause of death due to malignancy, with over 13,000 deaths reported in 1998.³ Around 35,000 new cases of the disease were reported in 1996.³

The aetiology of breast cancer is unclear, although it is likely that hormonal and genetic factors play a role.⁴ The incidence of breast cancer increases with age, doubling every year up until menopause.¹ Risk factors include early age of first menarche, later age of first full term pregnancy, late menopause and a family history of breast cancer.⁵

Figures suggest that between 16-20% of women initially presenting with breast cancer have advanced disease with distant metastases⁶ and around 50% of patients presenting with early or localised breast cancer will eventually progress to develop advanced or metastatic disease.^{7,8}

The risk of metastatic breast cancer (MBC) (stage IV, see Appendix 3) relates to known prognostic factors in the original primary tumour. These factors include oestrogen receptor negative disease, primary tumours 3cm or more in diameter and axillary node involvement.¹ The findings of a systematic review showed that recurrence occurred within 10 years of adjuvant chemotherapy for early breast cancer in 60-70% of node positive women and 25-30% of node negative women.¹

The prognosis of MBC depends on age, extent of disease, oestrogen receptor status,¹ and previous chemotherapy treatment. Some breast tumours contain a mutation in the human epidermal growth factor receptor 2 (HER2) oncogene (also known as C-*erbB-2*) which causes cells to make abnormally high amounts of HER2 protein (overexpression), which appears as a receptor on the surface of the cell.⁹ These receptors are involved in the regulation of cell growth. There is evidence that overexpression of the product of the HER2 oncogene is also associated with a poor

prognosis, indicating a more aggressive form of the disease, with a more rapid progression and shortened survival time.¹⁰

Approximately 25-30% of women with breast cancer have been found to overexpress the HER2 protein.^{11, 12} Recently published UK HER2 guidelines recommend that all patients with MBC should be tested for HER2 status using a diagnostic test based on immunohistochemistry (IHC) assays and that patients with borderline HER2 positive test (HER2 2+) should have this confirmed with a test based on gene amplification techniques, known as fluorescent in-situ hybridisation (FISH) test.¹³

Metastatic breast cancer is considered to be incurable. Median survival after diagnosis of advanced breast cancer (stage III or IV) has been reported to be 18-24 months.⁶ The median survival of patients with MBC overexpressing HER2 is further reduced by up to 50%.⁸ In women who receive no treatment for metastatic disease, the median survival from diagnosis of metastases is 12 months.¹ For most patients with metastatic disease treatment provides only temporary control of cancer growth.¹⁴ Treatment is therefore usually focused on relieving symptoms and improving the quality of life with as little treatment-related toxicity as possible.

2.2 CURRENT SERVICE PROVISION

The choice between endocrine therapy or chemotherapy and the selection of a specific drug regimen for first-line treatment of MBC is based on a variety of clinical factors such as: hormone receptor status, what drugs have already been given as adjuvant treatment, the likelihood of benefit balanced against the adverse event profile of the given drug, and the given drug's tolerability.¹

First line therapy for MBC usually consists of cyclophosphamide plus methotrexate plus fluorouracil (CMF) or an anthracycline-containing regimen. However, a patient is unlikely to respond well to a drug given previously as adjuvant therapy.⁸ A short disease-free interval (e.g. less than one year) between surgery and adjuvant therapy and the development of metastases suggests that the MBC is likely to be resistant to the adjuvant drug used.¹ This means that other agents need to be considered for first-line treatment of MBC.

In addition, an emerging problem is a sub-group of women with good performance status, who have not responded to anthracycline based combination therapy as first-line treatment for MBC, or have relapsed within a few months of adjuvant chemotherapy.

Trastuzumab is a fairly new anti-cancer agent that may be a useful addition to the drugs available for the treatment of MBC. Trastuzumab may be beneficial in a specific group of patients who are identified as having tumours that strongly overexpress HER2. The data available regarding these possible clinical uses are appraised in this report.

2.3 DESCRIPTION OF TECHNOLOGY

Identification of patients and criteria for treatment

Trastuzumab is used in patients with MBC who have tumours that overexpress HER2. Although around 25% of MBC patients overexpress HER2, only approximately 15% of MBC patients strongly overexpress HER2 (at the 3+ level) and it is this group of patients which form the well defined potential target population for trastuzumab therapy.⁸

When using the IHC analysis, the scoring of the level of HER2 overexpression depends on the percentage of cells stained, the intensity of the staining, or a combination of both parameters.¹⁵ Scores of 2+ and 3+ indicate weak and strong overexpression of HER2, respectively. A score of 2+ is considered to indicate that more than 10% of tumour cells have weak-to-moderate staining of the entire cell membrane for HER2, and a score of 3+ means that 10% of tumour cells have more than moderate staining for HER2.¹⁶ Alternatively, 25 to 50% of tumour cells with cytoplasmic membrane staining is considered to represent a score of 2+ and >50% of tumour cells with cytoplasmic membrane staining represents a score of 3+.¹⁷

Intervention

Trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) is a recombinant humanised monoclonal antibody that specifically targets the HER2 protein. Its activity is thought to be explained by at least three mechanisms of action: The antibody may (1) antagonise the function of the growth-signalling properties of the HER-2 system; (2) signal immune cells to attack and kill tumour cells; and (3) increase chemotherapy-induced cytotoxicity.¹⁸

Current indications for trastuzumab

In August 2000, trastuzumab was granted a European license for the treatment of HER2 overexpressing MBC (at the IHC HER2 3+ level):

- as a monotherapy in patients who have received at least two chemotherapy regimens for metastatic disease (i.e. third line or subsequent therapy for MBC). Prior chemotherapy must have included at least an anthracycline and a taxane unless patients are unsuitable for these treatments. Hormone receptor positive patients must also have failed hormonal therapy, unless patients are unsuitable for these treatments.
- in combination with paclitaxel for patients who have not received chemotherapy for metastatic disease and in whom an anthracycline is unsuitable (i.e. first line therapy for MBC, which means individuals may have received previous chemotherapy in the adjuvant setting for early breast cancer).⁸

The basic NHS price of trastuzumab is £407.40 per 150mg vial. This equates to an average cost for a typical patient receiving monotherapy treatment of £5,296 and for a patient receiving combination therapy of £15,481.⁸

Summary of current manufacturers information provided for health professionals¹⁹

Recommended dosage

An initial loading dose of 4mg/kg body weight and subsequent weekly doses of 2mg/kg body weight (beginning one week after the loading dose), administered as a 90-min intravenous infusion. If the initial loading dose is well tolerated subsequent doses may be administered over 30 minutes (see Special warnings and special precautions for use). Administration should continue until disease progression. When administered in combination with paclitaxel, paclitaxel may be given on the day after the first dose of trastuzumab or immediately following subsequent doses if trastuzumab is well tolerated.

Contra-indications

- Hypersensitivity to trastuzumab, murine proteins or any of the excipients.
- Severe dyspnoea at rest due to complications of advanced malignancy or requiring supplementary oxygen therapy.

- Avoid during pregnancy unless potential benefit to mother outweighs potential risk to the foetus.

Special warnings and special precautions for use

- Trastuzumab should not be administered as an intravenous push or bolus.
- Patients should be observed for symptoms such as fever or chills (or other infusion-related symptoms) for at least 6 hours after the start of the first infusion (2 hours for subsequent infusions). Emergency equipment must be made available.
- HER2 overexpression testing must be performed in a specialised laboratory prior to treatment.
- Due to a high risk of cardiotoxicity trastuzumab and anthracyclines should not be used in combination except in the setting of a well-controlled clinical trial with cardiac monitoring.

Adverse effects

Trastuzumab is associated with an increased risk of heart dysfunction. A recent editorial stated that trastuzumab should not be given to any woman who has had any prior problems with their heart muscle, including those with high blood pressure or a high cholesterol level.²⁰

A number of other serious adverse reactions have been reported in patients treated with trastuzumab alone or in combination with other chemotherapeutic agents. These include infusion-related symptoms, allergic/hypersensitivity reactions, serious pulmonary events, haematological toxicity, hepatic/renal toxicity, diarrhoea and an increased risk of infections.

3. EFFECTIVENESS AND COST-EFFECTIVENESS

3.1 METHODS OF THE REVIEW

Search strategy

The following databases were searched for relevant literature:

- MEDLINE
- EMBASE
- Cancerlit
- BIOSIS
- Index to Scientific and Technical Proceedings
- Cochrane Controlled Trials Register (CCTR)
- Database of Abstracts of Reviews of Effectiveness (DARE)
- NHS Economic Evaluation Database (NHSEED)

More detailed information about the search strategy is presented in Appendix 1.

Bibliographies of all included articles were searched for additional references. Manufacturer and sponsor submissions made to NICE were also reviewed to identify additional studies. The internet was searched for information on ongoing trials.

Inclusion and exclusion criteria

Titles (and where possible abstracts) of studies identified from all searches and sources (see Appendix 1) were assessed independently by two reviewers for relevance. If either reviewer considered the paper to be potentially relevant, a full paper copy of the manuscript was obtained. Each full paper copy was reassessed for inclusion using the following criteria. Studies that did not meet all of the criteria were excluded and their bibliographic details are listed in Appendix 2, along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in Appendix 10. Any disagreements were discussed in order to obtain a consensus and if no agreement was reached a third reviewer was consulted.

Interventions

The following interventions were included in the initial review:

Trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) alone or in combination with other agents versus systemic therapy without trastuzumab.

No RCTs of trastuzumab used as a single agent were found. Therefore, studies evaluating the use of trastuzumab used as monotherapy versus no other systemic therapy or trastuzumab used at a different dose were included in an update of the review.

Participants

Patients with breast cancer, encompassing all stages of disease, were included. Where possible the stage of disease was defined using the Simplified UICC staging system (see Appendix 3).

For the update section of the review only participants who had breast cancer overexpressing HER2 at level 3+, which had been previously treated with an anthracycline and/or a taxane, or those for whom these treatment were unsuitable were included in the review.

Study design

The ultimate standard for the evaluation of medical treatments is the randomised controlled phase III clinical trial.²¹ For the evaluation of clinical effectiveness, only randomised controlled trials (RCTs) were initially included in the review.

For the update section of the review that evaluated the use of trastuzumab used as monotherapy, non-randomised studies such as cohort studies, case-control studies and case-series were included. However, the findings of these studies should be interpreted with caution because, in contrast to high-quality RCTs, confounding and selection bias often distorts the findings of observational studies.²²

To evaluate the cost-effectiveness of trastuzumab and vinorelbine the following economic evaluations were considered:

Cost effectiveness analysis (CEA) (including cost-minimisation analysis (CMA) and cost consequence analysis (CCA))

Cost-utility analysis (CUA)

Cost-benefit analysis (CBA)

Outcome measures

The following outcome measures were included in the review:

Response (including complete and partial response)

Progression free survival

Overall survival

Symptom relief

Quality of life

Adverse effects (haematological toxicity including neutropenia, thrombocytopenia, anaemia; non-haematological toxicity including nausea, diarrhoea, constipation, stomatitis, abdominal pain, fatigue, asthenia, alopecia, anorexia, malaise and hyperbilirubinaemia; and any other adverse effects judged to be appropriate)

Cost

Data extraction strategy

Data extraction was conducted by one reviewer using predefined data extraction forms in a Microsoft Access database and checked by a second reviewer. Any disagreement was resolved by consensus and if this was not reached a third reviewer was consulted. Due to time constraints, only studies reported in English (for both effectiveness and economic data), German, Dutch and French (for effectiveness data only) were included in the report. However, the search strategy included all languages and the bibliographic details of non-English language studies are presented in the table of excluded studies (Appendix 2).

The following types of data were extracted and summarised: specific details about the interventions, the population investigated and the outcome measures used. Studies that have been reported in multiple publications were collated and reported only once.

Where sufficient data were presented an estimation of the treatment effect along with the 95% confidence interval (CI) was calculated for each individual study. Where possible this was done on an intention to treat basis. For dichotomous outcome measures the relative risk (RR) was calculated. For time to event outcomes (e.g. survival) hazard ratios (HR) were reported if given in the paper as well as median values and any measures of variance presented.

In order to assess the economic data in terms of the clinical effectiveness of the intervention (i.e. the direction of the cost-effectiveness data and the magnitude of effectiveness data), each study was given a summary grading (A-I) according to the level and direction of dominance (i.e. whether the intervention of interest should be preferred over the comparator). Extended dominance indicates that both the effectiveness data and the economic data support the use of either the intervention or the comparator and the decision on resource allocation is clear. When only the economic or the effectiveness data supports the intervention/comparator, the dominance is said to be partial or weak and a decision can still be made. However, if there is no dominance indicated then further incremental cost analysis may be required in order to estimate the incremental cost-effectiveness ratio. This is important in helping the decision-making process. The following matrix (Figure 1) illustrates all of the possible permutations, and was used to assign each study a summary grading.

Figure 1 Incremental cost of treatment compared to control^{23, 24}

		Health outcomes		
		+	o	-
Costs	+	A	B	C
	o	D	E	F
	-	G	H	I

	Strong dominance for decision in either direction (i.e. in favour of the intervention or comparator)
	Weak dominance for decision
	Non-dominance; no obvious decision

Code	Implication for intervention	Direction of the cost-effectiveness data and the magnitude of effectiveness data
A	Trade off	Higher costs but better outcomes (incremental analysis required)
B	Reject	Higher costs and no difference in outcomes (partial dominance in favour of the comparator)
C	Reject	Higher costs and poorer outcomes (extended dominance in favour of the comparator)
D	Accept	No difference in costs and improved outcomes (partial dominance in favour of the intervention)
E	Neutral	No difference in costs and no difference in outcomes
F	Reject	No difference in costs and poorer outcomes (partial dominance in favour of comparator)
G	Accept	Lower costs and improved outcomes (extended dominance in favour of the intervention)
H	Accept	Lower costs and no difference in outcomes (partial dominance in favour of the intervention)
I	Trade off	Lower costs but poorer outcomes (incremental analysis required)

Quality assessment strategy

The methodological quality of each included study was assessed using predefined checklists. Two reviewers conducted this process independently. Any

disagreements were resolved by consensus and a third reviewer was consulted if required.

Methods of analysis/synthesis

Results of data extraction and quality assessment are presented in structured tables and also as a narrative summary. Studies were grouped according to the type of intervention (monotherapy or combination therapy).

Included studies varied with regards to the type of intervention, therapy (1st or 2nd/3rd line), dosage regimen used, and study design. No formal statistical analysis of heterogeneity was undertaken due to the limited number of included studies. Due to heterogeneity (based on the judgement of the differences mentioned above) being present, pooling of the results was deemed inappropriate.

It was not possible to investigate the extent of publication bias due to the limited number of included studies. Sensitivity analyses were not undertaken for the same reason.

A narrative summary of the cost effectiveness data is presented, considering the methods of analysis used, the sources of effectiveness and cost data, the quality of the economic evaluation, and the generalisability of the findings to the UK setting. This section of the report also includes full economic evaluations that have been presented as part of the industry submission data sent to NICE (see Appendix 10).

3.2 EFFECTIVENESS

QUANTITY AND QUALITY OF RESEARCH AVAILABLE

Table 1: The evidence base for trastuzumab

	Number of trials	Number of economic evaluations
Trastuzumab as first line treatment	1 RCT combined therapy ¹⁶	1 combined therapy ⁸
Trastuzumab as first, second or third line treatment	2 case series ^{17, 25} and 1 RCT (both intervention groups received trastuzumab at different doses) monotherapy ²⁶	1 monotherapy ⁸

INCLUDED STUDIES

A summary of the included studies is presented in table 2.

Combination therapy

Only one RCT (Roche study H0648g) that investigated the use of trastuzumab as combination therapy was found that met the inclusion criteria.¹⁶ Study participants were randomised to receive chemotherapy alone or in combination with trastuzumab. The type of chemotherapy participants received was either paclitaxel or a combination of anthracycline (doxorubicin or epirubicin) and cyclophosphamide. This was dependent on whether participants had received prior adjuvant anthracycline or not. Participants who had received prior anthracycline (within the adjuvant setting for early breast cancer) were treated with paclitaxel. Prior to randomisation, participants were stratified according to the type of chemotherapy regimen they had received within the adjuvant setting.

The study population of the trial evaluating trastuzumab as combination therapy included women with overexpressing HER2 MBC at level 2+ or 3+ as determined by immunohistochemistry (IHC), who had not received prior treatment for MBC.¹⁶ The number of participants included in the trial was 469.

Trastuzumab was administered at a loading dose of 4mg/kg and then 2mg/kg intravenously every week. The dosage for the chemotherapy regimen was doxorubicin 60mg/m² intravenously, epirubicin 75mg/m² intravenously, cyclophosphamide 600mg/m² intravenously and paclitaxel 175mg/m² intravenously over 3 hours, given every 3 weeks. The number of cycles of chemotherapy regimens used in both treatment groups was 6. Trastuzumab was administered until there was evidence of disease progression. The mean number of doses of trastuzumab was 36 (range 1 to 98).

The primary endpoint was time to disease progression and secondary endpoints included response rate, duration of response, time to treatment failure, survival and quality of life.

The final analysis of the primary endpoint, time to disease progression, was performed nine months after the enrolment of the last patient (cut-off date of 31 December 1997). Survival was analysed 31 months after enrolment ended (cut-off date of October 1999). The Median duration of follow-up was 30 months (range 30 to 51).

For ethical reasons, at the time of disease progression, participants were allowed to enrol into the follow-on protocol H0648g that permitted all patients to receive trastuzumab. Seventy-five percent of the HER2 3+ level sub-group who were initially randomised to receive paclitaxel alone underwent a treatment switch to trastuzumab.⁸

Monotherapy

There were no RCTs found that met the initial inclusion criteria, which evaluated trastuzumab as a monotherapy versus systemic therapy without trastuzumab in participants who had received at least two chemotherapy regimens for metastatic disease.

The new update searches revealed three studies that met the new inclusion criteria for trastuzumab as monotherapy. These included two case series (study H0551g¹⁷ and study H0649g)²⁵ and one RCT (study H0650g),²⁶ where trastuzumab was administered in both intervention groups).

Two studies (H0551g¹⁷ and H0650g)²⁶ included women with MBC and one study (H0649g)²⁵ looked at women with advanced breast cancer. All three studies included women whose breast cancer overexpressed HER2 at level 2+ or 3+ as determined by IHC. The number of participants who had a tumour overexpressing HER2 at level 3+ included 39 out of 46 (85%) women in study H0551g,¹⁷ 172 out of 222 (77%) in study H0649g,²⁵ and 85 out of 113 (75%) in study H0650g.²⁶

Two studies included participants who had received previous treatment with an anthracycline and/or taxane. Study H0649g included 201 (94%) women who had been pre-treated with anthracycline and 143 (67%) women who had previously received taxane therapy.²⁵ One hundred and forty six (68%) women had received prior adjuvant chemotherapy and 214 (98%) had received prior chemotherapy for MBC. For study H0650g, 62 (55%) women had received previous anthracycline therapy and that 76 (68%) women had received prior adjuvant chemotherapy.²⁶ It was not stated in what setting the anthracycline therapy had been administered. Baselga et al. reported that for study H0551g, 26 (57%) women had received previous adjuvant chemotherapy, 4 (8.7%) had received prior neoadjuvant chemotherapy and 38 (83%) had received prior chemotherapy for MBC.¹⁷ It was not stated how many of these women had been pre-treated with anthracycline and/or taxane therapy.

For study H0551g, participants received a loading dose of 250mg of trastuzumab intravenously followed by 10 weekly doses of 100mg.¹⁷ Participants with no disease progression at the completion of this treatment period were offered a maintenance dose of 100mg/week. In study H0649g the loading dose used was 4mg/kg followed by a 2mg/kg maintenance dose.²⁵ If participants developed disease progression, the investigators could continue with 2mg/kg or discontinue treatment. For study H0650g, participants were randomised to receive either trastuzumab at the standard lower dose regimen which included an initial dose of 4mg/kg followed by 2mg/kg intravenously weekly, or a higher dose regimen of 8mg/kg loading and 4mg/kg weekly until disease progression.²⁶

The primary endpoint for studies H0649g²⁵ and H0551g¹⁷ was response, and for study H0650g²⁶ the primary endpoints were response and adverse effects.

The duration of follow-up was not stated in one study.¹⁷ The median follow up in the remaining two studies included 12.8 months (range not given) in study H0649g²⁵ and 11 months (range 1.2 to 35 months) in study H0650g.²⁶

Table 2: Trastuzumab - summary of included studies

Trial source	Accrual dates	No. of participants	Type of therapy	Intervention	Control
Trastuzumab as combination therapy					
Study H0648g Roche report (included confidential data), ⁸ published paper by Slamon et al. ¹⁶ and meeting abstracts ²⁷⁻³¹	June 1995 to March 1997	469	1 st line	Trastuzumab plus chemotherapy (either cyclophosphamide + anthracycline or paclitaxel)	Chemotherapy alone (either cyclophosphamide + anthracycline or paclitaxel)
Trastuzumab as monotherapy					
Study H0551g Two published papers by Baselga et al. ^{17, 32} and a non systematic review of trastuzumab studies published by Baselga, 2000. ³³ Accrual dates were obtained from Shak, 1999 ³⁴	March 1993 to June 1994	46	Not stated (82.6% had received prior chemotherapy for MBC)	All participants received trastuzumab	None
Study H0649g Published paper by Cobleigh et al., 1999 ²⁵ Roche report, ⁸ and an abstract published by Cobleigh, 1999 ³⁵ (Information (quality of life data) on the study was also presented in Osoba & Burchmore, 1999 ³⁰ and in an abstract by Lieberman et al., 1999) ³⁶ Interim results were presented in as an abstract by Cobleigh et al., 1998. ³⁷	April 1995 and September 1996	222	2 nd or 3 rd line therapy	All participants received trastuzumab	None
Study H0650g Published papers by Vogel et al. ²⁶ Information on this study was also presented as an abstract (Vogel et al., 2000). ³⁸ However, the results in the two publications differed	October 1995 to May 1998	113	1 st line therapy	Trastuzumab at a standard lower dose regimen.	Trastuzumab at a higher dose regimen.

and therefore only information from the published paper is used in the review. Accrual dates were obtained from Shak, 1999 ³⁴					
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EXCLUDED STUDIES

During the initial searches nineteen studies were ordered as full papers and then excluded when the inclusion criteria were applied by two reviewers independently (see Appendix 2). Five were non-systematic reviews of treatment for breast cancer,³⁹⁻⁴³ one was a report of pooling of safety data from three trials,³¹ eight were trials of trastuzumab which did not include a control group,^{18, 25, 35, 44-48} two were preclinical trials which did not involve human participants,^{49, 50} one was an evaluation of changing levels of HER2 in patients treated with paclitaxel⁵¹ and one was not a drug trial.⁵²

During the update searches (to identify studies of trastuzumab used as monotherapy only) 17 studies were ordered as full papers and then excluded whilst applying the inclusion criteria. This included a phase I dose escalation study of trastuzumab in 18 patients with MBC overexpressing HER2.⁵³ The study included response as an outcome measure. However, it was excluded because tumours were considered to overexpress HER2 if at least 10% of tumour cells had positive membrane staining (HER2 overexpression at level 2+ means that 25-50% of tumour cells have positive staining)¹⁷ and the number of participants with HER2 overexpression at level 3+ was not reported. Thirteen excluded studies were unsystematic reviews looking at the use of trastuzumab for the treatment of breast cancer,^{33, 54-64} one was a review looking at trial desing,⁶⁵ one was a study investigating the level of the HER2 overexpression in a cohort of women with breast cancer,⁶⁶ one was a study that compared serum and tissue HER2 overexpression in MBC prior to trastuzumab therapy,⁶⁷ and one was a study that looked at the effect of trastuzumab on cellular DNA and cell cycle.⁶⁸

Information on two phase I studies was received from Roche.⁸ Both studies included participants with advanced cancer (with proven metastatic spread refractory to any available curative therapy). Because they were phase I studies (usually used to determine the dose related tolerability and safety in humans and drug absorption and distribution pharmacokinetics),⁶⁹ the main outcome measures were adverse events and pharmacokinetic data, although response rates were also reported. However, this information was not presented according to cancer type and these studies were therefore excluded. **Commercial in confidence information removed from paragraph.**

QUALITY OF INCLUDED STUDIES

Combination therapy

A summary of the quality of the included trastuzumab trial is presented in table 3 that relates to the checklist presented in Appendix 4.

Randomisation

The randomisation procedure used by the trastuzumab trial was considered to be adequate and the number of participants initially randomised was stated along with the number of participants included in the analysis.⁸ Allocation was also thought to

have been concealed. **Commercial in confidence information removed from paragraph.**

Baseline details

Reported baseline characteristics included the number of participants who had received prior adjuvant therapy (chemotherapy, hormonal therapy and radiotherapy), mean age (and age range) of the participants, Karnofsky score, the number of participants who had level 3+ HER2 overexpression, the mean number of positive lymph nodes at diagnosis, and the number of metastatic sites at enrolment. The median disease free interval at baseline was also reported. Information relating to the baseline characteristics of participants in the trastuzumab and control group were reported according to the chemotherapy subgroups (i.e. participants treated with anthracycline and cyclophosphamide or those who received paclitaxel).

There was general comparability between the treatment groups at baseline with regard to most of the characteristics reported. However, 57% of participants who were allocated to trastuzumab plus anthracycline chemotherapy were reported to have received prior adjuvant chemotherapy compared to 37% of the participants allocated to receive anthracycline chemotherapy without the addition of trastuzumab. It was not reported how this difference was handled in the analysis.

Eligibility criteria

A summary of the trial's inclusion/exclusion criteria were presented in the published paper.¹⁶ This information was presented in full within the industry submission data which was marked confidential.

Co-interventions stated

It was not stated if any of the participants were taking any other medications whilst in the trial.

Blinding

During the initial conduct of the trial, participants in the control arm received weekly 90 minute placebo infusions followed by an observational period.⁶⁵ This was not only considered to be inconvenient but it was also thought to put the patients at an unnecessary increased risk of infection and other complications. The study was therefore modified to an open-label design, which means that neither the participants or physicians were blinded.

Responses to treatment were confirmed by an independent Response Evaluation Committee (REC). Members of the REC were blinded to the treatment group assignment. The REC assessed tumor response in 99% of the 452 patients who had an assessment after base-line evaluation and 95% of the 469 patients who were enrolled in the study. **Commercial in confidence information removed from paragraph.**

The success or otherwise of the blinding procedure was not reported to have been checked.

Follow up

Less than 20% of participants were reported to have been lost to follow-up at the end of the trial.

Five randomised participants were reported to have discontinued on the first day of the trial, prior to receiving any of the intervention treatment. The reasons for

withdrawal included death (n=1), disease progression as determined by the investigator (n=1), participant request (n=2), and inadvertent enrolment (n=1).

Reporting of outcomes for withdrawals

Overall 92% (215/234) of participants receiving chemotherapy alone and 74% (173/235) receiving trastuzumab and chemotherapy were reported to have discontinued from the trial in March 1997. The reason for discontinuation was presented according to the allocated treatment group assignment, within the Roche report (marked commercial in confidence) and all participants were included in the final analysis.⁸ At the time of disease progression, participants were allowed to enrol on the follow-on protocol (study H0659g) where all participants were permitted to receive trastuzumab. **Commercial in confidence information removed from paragraph.**

Intention to treat analysis (ITT)

Efficacy analysis was conducted using the ITT approach. **Commercial in confidence information removed from paragraph.**

Overall quality of the trastuzumab plus chemotherapy RCT

The overall quality of the trial was considered to be moderate to high. The randomisation procedure was adequate and allocation was concealed. Not all important baseline characteristics were considered to have been collected (disease bulk, number of previous regimens, histology and performance status were not reported). Baseline comparability was also not achieved for previous anthracycline therapy and it was not stated how this was handled in the analysis. The eligibility criteria were clearly reported and the blinding of outcome assessors was partially achieved. However, the success of blinding was not checked. More than 80% of participants withdrew but were not considered lost to follow-up. An ITT analysis was undertaken.

Table 3: Quality of the included trastuzumab combination therapy trial (according to the checklist presented in appendix 4)

Study	Sample size (arms)	Random. procedure adequate	Allocation concealed	No. Random stated	Baseline details	Baseline comp. achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of administrators	Participants blinded	Success of blinding checked	Follow up ≥80%	Outcomes of withdrawals	ITT
Trastuzumab as combination therapy															
Slamon et al., 1999 ¹⁶ Study HO648g	469 (2)	✓	✓	✓	✓/x	x	✓	x	✓/x	x	x	x	✓	✓	✓

✓ = Yes; x = No; ✓/x = Partially covered; ? = not stated, not enough information or unclear; NA= not appropriate.

Monotherapy

A summary of the quality of the included trastuzumab monotherapy studies are presented in table 4 ad 5, which relate to the checklists presented in Appendix 4.

Representative sample

All three studies were considered to have used a representative sample selected from a relevant population. However, one study (H0551g) did not report how many participants had received prior anthracycline and/or taxane therapy or alternatively, the number of women for whom these treatments were unsuitable.¹⁷ The remaining two studies also did not report how many women these treatments were unsuitable for, and one study (H0650g) did not report whether any participants had received prior taxane therapy.²⁶ Both studies failed to specify whether these previous therapies had been used in the adjuvant setting or for the treatments of MBC.^{25, 26}

Explicit inclusion criteria

All three studies presented a list of inclusion and exclusion criteria that were relatively similar. These lists were not extensive thus allowing relatively broad selection criteria.

Individuals entering the survey at a similar time point

All three studies included women with advanced MBC. However, for two studies (H0551g¹⁷ and H0649g),²⁵ there were slight variations within individual study populations with regards to some baseline characteristics (e.g. number of metastatic sites,^{17, 25} number of lymph nodes at primary diagnosis,²⁵ and disease-free interval)²⁵ that relate to the severity or progression of the disease. The disease free interval was not reported for study H0551g.¹⁷ For study H0650g (a RCT of trastuzumab used at two different dosage regimens), the baseline characteristics were presented for the study population as a whole, and not according to the randomised groups.²⁶ In addition, for each characteristic, only the number and percentage of participants within a sub group were reported and therefore, it was not easy to assess whether the participants entered into the study at a similar point in their disease progression. However, it is believed that this may not have been the case as just over one-quarter of the participants (27%) had a disease free-interval of less than 12 months and 30% of the participants had three or more metastatic sites.

Long enough follow-up

The median length of follow-up was 12.8 months (range not stated) for one study (H0649g)²⁵ and 11 months (range 1.2 to 35 months) in another (study H0650g).²⁶ The primary endpoint for both studies was response. Patient response is usually defined over a short term period in phase II studies, based on the underlying idea that short term response is a necessary precursor to improved survival and morbidity, which would then be evaluated in phase III RCTs.⁷⁰ The follow-up is therefore deemed to be long enough to demonstrate an estimated response associated with trastuzumab, but for assessing long-term patient response the follow-up period may not have been sufficient, although prognosis is generally poor in patients with MBC. The length of follow-up was not stated for study H0551g.¹⁷

Use of objective criteria and blinding to assess outcomes

The primary objective in all three studies was to measure response. The definition used to measure complete and partial response was only reported in two studies (H0551g¹⁷ and H0649g).²⁵ The investigators, as well as an independent response evaluation committee (REC), which was composed of an oncologist and a radiologist, assessed these outcomes. The

committee was reported to have been blinded in study H0649g²⁵ but not in study H0551g¹⁷. Antitumour response was evaluated by only the investigators in study H0650g, and no blinding was reported.²⁶ This means that the intervention measure of response may represent an overestimation, as demonstrated by study H0649g²⁵ which reported that although both the investigators and the REC identified the same number of complete response, a higher rate of partial response was reported by the investigators (11% vs 17%).

Description of sub-series and distribution of prognostic factors

Two studies (H0649g²⁵ and H0650g)²⁶ looked at the level of antitumour response within specific subseries of participants, including those with MBC overexpressing HER2 at level 3+. The baseline distribution of these characteristics were presented fully in tables for one study (H0649g)²⁵ and only partially reported in the second (although the total number of participants in each subgroup analysis was identified). It was not stated for study H0649g how many subseries analysis were undertaken in total, but the findings of those that were found to be significant were reported (tumours that overexpress HER2 at level 3+ and participants whose time to first relapse was greater than 6 months).²⁵ A multivariate logistic regression analysis was then conducted to evaluate if any of the baseline characteristics were an independent predictor of tumour response. Study H0650g was a RCT of trastuzumab administered as two different dosage regimens.²⁶ The overall response to treatment for both intervention groups combined were reported for participants with liver metastases, overexpression of HER2 at level 3+, prior adjuvant doxorubicin and prior stem-cell transplantation. The number of participants included in each subset was reported, but it was not stated how many were randomised to the different intervention groups and no comparison was made between the two intervention groups within any of these subgroups.

Quality of study H0650g according to the checklist for RCTs

As previously mentioned, study H0650g was a RCT of trastuzumab administered as two different dosage regimens.²⁶ The quality of the study, according to the checklist for RCTs was deemed to be poor. Information with regards to most of the included criteria was not reported. The method of randomisation was not reported and it was not stated if allocation had been concealed. It was not possible to assess whether the baseline characteristics of the two treatment groups were comparable because the demographic information was only presented for the population as a whole. It was not reported if any co-interventions were administered. The investigators, who were not reported to have been blinded, assessed outcome measures. The study was reported to have been single blind and therefore, the participants were considered to have been blinded to the dosage level of trastuzumab that they received. However, as all participants in the trial received trastuzumab it was not considered that they had been blinded to the intervention. The outcomes of those who withdrew from the study were not reported.

Overall quality of the trastuzumab monotherapy studies

The overall quality of the three studies according to the quality checklist for case series was found to be moderate. All three studies were considered to have used a representative sample selected from a relevant population. All three studies reported a summary of their inclusion and exclusion criteria that were relatively similar. All three studies included women with advanced MBC, but there were slight variations within individual study populations with regards to some baseline characteristics relating to disease progression. The follow-up period was only reported by two studies (H0649g²⁵ and H0650g).²⁶ The primary objective in all three studies was to measure response. The follow-up was considered to be long enough to demonstrate an estimated response associated with trastuzumab, but may not have been sufficient for assessing long-term patient response, although prognosis is generally poor in patients with

MBC. The definition used to measure complete and partial response was only reported in two studies (H0551g¹⁷ and H0649g).²⁵ The investigators, as well as an REC, assessed these outcomes. The committee was reported to have been blinded in study H0649g²⁵ but not in study H0551g.¹⁷ Antitumour response was evaluated by only the investigators in study H0650g, and no blinding was reported.²⁶ Two studies (H0649g²⁵ and H0650g)²⁶ undertook a comparisons of subseries, where sufficient description of the series and the distribution of prognostic factors was only considered within one study (H0649g).²⁵ The one included study that was a RCT, when assessed according to the quality checklist for RCTs was considered to be of poor quality.²⁶

Table 4: Quality of the included trastuzumab monotherapy studies (according to the checklist presented in appendix 4)

Study	Sample size	representative sample	Explicit inclusion	Individuals enter the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the sub-series and the distribution of prognostic factors?
Trastuzumab as monotherapy							
Baselga et al., 1996 ¹⁷ Study H0551g	46	✓	✓	✓/x	?	✓/x	NA
Cobleigh et al., 1999 ²⁵ Study H0649g	222	✓	✓	✓/x	✓/x	✓	✓
Vogel et al., 2001 ^{26**} Study H0650g	113	✓	✓	?	✓/x	x	x

Items were graded in terms of ✓ yes (item properly addressed), x no (item not properly addressed), ✓/x partially (item partially addressed), ? unclear or not enough information, or NA not applicable.

**Study H0650g was a RCT where both intervention groups received trastuzumab (at different dosage regimens). In order to be able to compare the quality of this trial with that of the remaining two phase II studies this trial has also been quality assessed according to the above criteria.

Table 5: Quality of the included trastuzumab monotherapy trial (according to the checklist presented in appendix 4)

Study	Sample size (arms)	Random. procedure adequate	Allocation concealed	No. Random stated	Baseline details	Baseline comp. achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of administrators	Participants blinded	Success of blinding checked	Follow up ≥80%	Outcomes of withdrawals	ITT
Trastuzumab as monotherapy therapy															
Vogel et al., 2001 ²⁶ Study H0650g	113 (2)	?	?	✓	x	?	✓/x	x	?	?	✓ (to dosage level only)	x	✓	x	x

✓ = Yes; x = No; ✓/x = Partially covered; ? = not stated, not enough information or unclear; NA= not appropriate.

ASSESSMENT OF EFFECTIVENESS

Combination therapy

Information in the publication of the trial included subgroup analysis of the specific type of chemotherapy agent used (anthracycline or paclitaxel) and the level of HER2 overexpression (level +3 or level +2). The recommended use of trastuzumab in the UK as first line therapy is in combination with paclitaxel in participants with level 3+ overexpressing MBC. The results of the subset analysis relating to participants with level 3+ overexpressing MBC are presented for survival outcomes. However, it is important to note that the number participants in each subgroup was small and HER2 overexpression level was not specified as a stratification variable from the randomisation procedure. Randomisation was stratified according to the type of chemotherapy regimen participants were receiving. The number of participants in the two intervention groups receiving paclitaxel was therefore comparable at baseline (trastuzumab plus paclitaxel treatment group n = 92, paclitaxel only treatment group n= 96). Where given, the results of the subgroup analysis relating to paclitaxel therapy are presented.

The data cut-off point for the main analysis was reported to have been the 31 December 1997 for which the minimum follow-up period was 9 months (participants were enrolled between June 1995 and March 1997). The data relating to a final analysis of survival was based on the cut-off date October 1999 (31 months after the enrollment of the last patient, median follow-up of 35 months (range 30 to 51).

Response

Complete response was defined as the disappearance of all radiographically and/or visually apparent tumour. Partial response was defined as a reduction of at least 50% (but less than 100%) in the sum of the products of the perpendicular diameters of all measurable lesions. The overall tumour response was defined as complete or partial response. **Commercial in confidence information removed from paragraph.**

A two-sided χ^2 test was used to compare the overall response rates between the two treatment groups. **Commercial in confidence information removed from paragraph.**

Progressive disease was defined as an increase of 25% or more of any measurable lesion and/or death and the commencement of other anti-tumour therapy or discontinuation of treatment were incorporated into the definition of treatment failure.

There was no significant difference between the two chemotherapy treatment groups with regards to complete response. Overall response was achieved in a significantly greater number of participants treated with trastuzumab (50%) compared to those treated with chemotherapy alone (32%). The results are presented in table 6 along with the relative risk and 95% confidence intervals (CIs).

Significantly fewer participants treated with trastuzumab plus chemotherapy were deemed to have progressive disease compared to those treated with chemotherapy alone. Treatment failure was also reported in a significantly greater number of participants treated with chemotherapy alone compared to those who received trastuzumab plus chemotherapy. The results along with RR with 95% CIs are presented in table 6.

Table 6 : Summary of tumour response for trastuzumab plus chemotherapy

Outcome	Trastuzumab n/N	Control n/N	Relative risk (95% CI)
Complete Response (CR) (RR >1 favours trastuzumab)	18/235	8/234	2.24 (1.02 to 4.96)
Overall tumour response (RR >1 favours trastuzumab)	118/235	74/234	1.59 (1.26 to 1.99)
Disease progression (RR <1 favours trastuzumab)	C-I-C	C-I-C	0.51 (0.41 to 0.63)
Treatment failure (RR <1 favours trastuzumab)	C-I-C	C-I-C	0.58 (0.47 to 0.70)

Eight percent (7/92) of participants in the trastuzumab plus paclitaxel treatment group had a complete response compared to 2% (2/96) of those treated with paclitaxel alone. This difference was not found to be statistically significant. When considering the overall response to treatment, the rate was doubled by the addition of trastuzumab to paclitaxel (41%, 95% CI: 31 to 51 versus 17%, 95% CI: 9 to 24). Treatment failure and disease progression was also found to be significantly less in participants treated with trastuzumab plus paclitaxel compared to paclitaxel alone.

Table 7: Summary of tumour response for trastuzumab plus paclitaxel

Outcome	Trastuzumab n/N	Control n/N	Relative risk (95% CI)
Complete Response (CR) (RR >1 favours trastuzumab)	7/92	2/96	3.65 (0.89 to 15.22)
Overall tumour response (RR >1 favours trastuzumab)	38/92	16/96	2.48 (1.49 to 4.12)
Disease Progression			0.38 (0.27 to 0.53)
Treatment failure (RR <1 favours trastuzumab)	C-I-C	C-I-C	0.46 (0.33 to 0.63)

Duration of response

Time to disease progression was defined as the time from randomisation until documented disease progression or death (whichever occurred first). Duration of major response was defined as the time from the initial complete or partial response to documented disease progression or death (whichever occurred first). Time to treatment failure was defined conservatively as disease progression, death, treatment discontinuation for any other reason or

initiation of new antitumour therapy. **Commercial in confidence information removed from paragraph.**

Kaplan-Meier survival methodology was reported to have been used to estimate the median time to disease progression, and median time to treatment failure for each treatment group. A two-sided log-rank test was used to compare the two treatment groups. **Commercial in confidence information removed from paragraph.**

The median time to disease progression was reported to be significantly shorter in the chemotherapy alone treatment group (4.6 months (95% CI: 4.4 to 5.4) compared to those who received chemotherapy with the addition of trastuzumab (7.4 months (95% CI: 7.0 to 9.0), $p < 0.001$). However the hazard ratio was not given and insufficient information was presented to calculate the hazard ratio or any measure of its variance. The Kaplan-Meier plot of time to disease progression was presented. **Commercial in confidence information removed from paragraph.**

The addition of trastuzumab was reported to have significantly increased the median duration of response from 6.1 (95% CI 5.5 to 7.8) months to 9.1 (95% CI 7.7 to 11.0) months ($p < 0.001$). However, no hazard ratio were presented and insufficient information was provided to calculate it. **Commercial in confidence information removed from paragraph.**

The median time to treatment failure was reported to be significantly higher in the trastuzumab plus chemotherapy treatment group (6.9 months, 95% CI: 6.0 to 7.3) compared to treatment with chemotherapy alone (4.5 months, 95% CI: 4.3 to 4.9), $p < 0.001$. Insufficient information was presented to calculate the hazard ratio.

Table 8: Summary of duration of response (months) for trastuzumab plus chemotherapy

Outcome	Trastuzumab N	Trastuzumab median (95% CI)	Control N	Control Median (95% CI)
<i>Median time to disease progression</i>	235	7.4 (7.0 to 9.0)	234	4.6 (4.4 to 5.4)
<i>Median duration of response</i>	235	9.1 (7.7 to 11.0)	234	6.1 (5.5 to 7.8)
<i>Median time to treatment failure</i>	235	6.9 (6.0 to 7.3)	234	4.5 (4.3 to 4.9)

As seen from table 10, the median time to disease progression for participants treated with trastuzumab plus paclitaxel was more than twice that of participants treated with paclitaxel alone ($p < 0.001$, using log rank test).

The median duration of response for participants treated with trastuzumab plus paclitaxel was over twice that of participants treated with paclitaxel alone ($p < 0.001$, using log rank test).

The median time to treatment failure of participants who received trastuzumab plus paclitaxel was twice that of participants who were treated with paclitaxel as a single agent ($p < 0.001$).

Table 9: Summary of duration of response (months) for trastuzumab plus paclitaxel

Outcome	Trastuzumab N	Trastuzumab (+paclitaxel)	Control N	Control (paclitaxel)
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		median (95% CI)		only median (95% CI)
Median time to disease progression	92	6.9 (5.3 to 9.9)	96	3.0 (2.1 to 4.3)
Median duration of response	92	10.5 (7.3 to 12.5)	96	4.5 (3.9 to 6.4)
Median time to treatment failure	92	5.8 (4.4 to 7.1)	96	2.9 (2.0 to 4.3)

Survival

Kaplan-Meier survival methodology was used to estimate median survival time for each treatment group and two sided log-rank tests were used to compare the two treatment groups.

The survival rate at 1 year was reported to be significantly greater for participants treated with trastuzumab plus chemotherapy than those treated with chemotherapy alone ($p < 0.05$). The median overall survival was also reported to be significantly improved when the trastuzumab combination was compared to chemotherapy alone ($p = 0.046$). Kaplan-Meier curves of overall survival were presented but the hazard ratio was not reported. **Commercial in confidence information removed from paragraph.**

Table 10: Summary of survival (months) for trastuzumab plus chemotherapy

Outcome	Trastuzumab N	Trastuzumab median (95% CI)	Control N	Control median (95% CI)	P value reported by authors
Median survival time	235	25.1 (22.2 to 29.5)	234	20.3 (16.8 to 24.2)	P=0.046
C-I-C					
C-I-C	C-I-C	29.1 (24.1 to 35.6)	C-I-C	20.3 (15.7 to 23.9)	P<0.05
C-I-C	C-I-C	C-I-C	C-I-C	C-I-C	

Table 11: Summary of mortality rates at 1 year for trastuzumab plus chemotherapy

Outcome	Trastuzumab Rate (%) (n=235) (HER2 3+ n=176) (HER2 2+ n=59)	Control Rate (%) (n=234) (HER2 3+ n=173) (HER2 2+ n=61)	
Survival at 1 year	79.1	68.4	P<0.05

Commercial in confidence information removed from table.

Confidence intervals were computed using the normal approximation to binomial distribution p-values were based on Pearson's chi-square

Table 12: Summary of patient deaths for trastuzumab plus chemotherapy

Commercial in confidence information removed from table.

Seventy-two percent (69/96) of participants in the paclitaxel alone group received trastuzumab on disease progression. There was no significant difference between the two treatment groups

with regard to median survival time (p=0.17). There was also no significant difference between the two treatment groups with regard to survival at 1 year. The results are presented in table 13 and 14.

Table 13: Summary of survival (months) for trastuzumab plus paclitaxel

Outcome	Trastuzumab +paclitaxel N	Trastuzumab +paclitaxel median (95% CI)	Control N	Control median (95% CI)	P value reported by authors
<i>Median survival</i>	92	22.1 (16.9 to 28.6)	96	18.4 (12.7 to 24.4)	P=0.17
C-I-C	C-I-C	25	C-I-C	18	

Table 14: Summary of mortality rates at 1 year for trastuzumab plus paclitaxel

Outcome	Trastuzumab +paclitaxel Rate % (95% CI) (n=92)	Paclitaxel alone Rate % (95% CI) (n=96)	P value reported within publication
C-I-C	C-I-C	C-I-C	RR of death = 0.80 (0.56 to 1.11)
<i>Survival at 1 year</i>	72.8	61.5	
C-I-C	C-I-C	C-I-C	C-I-C

Confidence intervals were computed using the normal approximation to binomial distribution p-values were based on Pearson's chi-square

Toxicity

As seen from table 16, with the exception of heart failure, fever and alopecia there was no real difference between the treatment groups for any severe adverse events that occurred in more than 10% of the participants. The results are presented in table 16. Severe heart failure occurred in a greater number of participants treated with chemotherapy plus trastuzumab than those treated with chemotherapy alone (10% vs 2%). More participants treated with trastuzumab plus chemotherapy (8%) had a fever or pharyngitis than those in the control group (4%). Fewer participants treated with trastuzumab plus chemotherapy (26%) had alopecia compared to those treated with chemotherapy alone (35%). **Commercial in confidence information removed from paragraph.**

As seen from table 15 there was no significant difference between paclitaxel plus chemotherapy versus paclitaxel alone for any serious adverse events as reported by more than 10% of the participants. **Commercial in confidence information removed from paragraph.**

Twenty-five participants (19 in the subgroup given an anthracycline, cyclophosphamide plus trastuzumab and 6 in the subgroup given paclitaxel plus trastuzumab) discontinued trastuzumab due to an adverse event. It was not stated how many participants discontinued treatment in the control group due to adverse events. Eighteen participants (15 treated with trastuzumab plus anthracycline and 3 in the subgroup treated with paclitaxel and trastuzumab) had clinical signs of cardiac dysfunction. Two additional adverse events were attributed to trastuzumab therapy:

an embolic stroke as a possible complication of cardiac dysfunction and chest pain after 49 doses of trastuzumab and six cycles of an anthracycline and cyclophosphamide. The events in the remaining five patients were not considered to be related to trastuzumab.¹⁶ **Commercial in confidence information removed from paragraph.**

Table 15: Severe adverse events (that occurred in more than 10 percent of participants) for trastuzumab plus chemotherapy

Outcome	Trastuzumab (n=234)	Control (n=230)	Relative risk (95% CI)
Any type			
<i>Abdominal pain</i>	3%	3%	0.98 (0.36 to 2.65)
<i>Asthenia</i>	7%	7%	0.98 (0.51 to 1.89)
<i>Back pain</i>	4%	4%	0.98 (0.41 to 2.36)
<i>Chest pain</i>	3%	4%	0.76 (0.30 to 1.95)
<i>Chills</i>	<1%	<1%	N/A
<i>Fever</i>	8%	4%	2.08 (0.98 to 4.42)
<i>Headache</i>	4%	4%	0.98 (0.41 to 2.36)
<i>Infection</i>	2%	2%	0.98 (0.31 to 3.14)
<i>Pain</i>	6%	7%	0.86 (0.44 to 1.70)
<i>Heart failure</i>	10%	2%	4.52 (1.82 to 11.36)
Digestive tract			
<i>Anorexia</i>	<1%	2%	N/A
<i>Constipation</i>	1%	3%	0.28 (0.07 to 1.17)
<i>Diarrhoea</i>	1%	3%	0.28 (0.07 to 1.17)
<i>Nausea</i>	5%	7%	0.74 (0.36 to 1.50)
<i>Stomatitis</i>	<1%	0%	N/A
<i>Vomiting</i>	5%	7%	0.74 (0.36 to 1.50)
Hematological and lymphatic systems			
<i>Anaemia</i>	2%	2%	0.98 (0.31 to 3.14)
<i>Leukopenia</i>	11%	9%	1.22 (0.71 to 2.09)
Musculoskeletal system			
<i>Arthralgia</i>	4%	2%	1.77 (0.63 to 4.97)
<i>Myalgia</i>	3%	3%	0.98 (0.37 to 2.65)
Nervous system			
<i>Parathesia</i>	<1%	<1%	N/A
Respiratory tract			
<i>Increased coughing</i>	<1%	<1%	N/A
<i>Dyspnea not related to heart failure</i>	3%	3%	0.98 (0.36 to 2.65)
<i>Pharyngitis</i>	0%	<1%	N/A
Skin			
<i>Alopecia</i>	26%	35%	0.75 (0.57 to 0.99)
<i>Rash</i>	<1%	<1%	N/A

*Excludes 5 participants who were never treated

Table 16: Severe adverse events (that occurred in more than 10 percent of participants) for trastuzumab plus paclitaxel

Outcome	Trastuzumab	Control	Relative risk (95% CI)
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	(n=91)	(n=95)	
Any type			
Abdominal pain	3%	4%	0.78 (0.20 to 3.05)
Asthenia	8%	8%	0.91 (0.36 to 2.33)
Back pain	8%	5%	1.46 (0.51 to 4.23)
Chest pain	3%	5%	0.63 (0.17 to 2.31)
Chills	1%	0%	N/A
Fever	2%	1%	2.09 (0.28 to 15.79)
Headache	7%	2%	3.13 (0.74 to 13.35)
Infection	1%	2%	0.52 (0.07 to 3.92)
Pain	10%	6%	1.57 (0.60 to 4.08)
Heart failure	2%	1%	2.09 (0.28 to 15.79)
Digestive tract			
Anorexia	1%	2%	0.52 (0.07 to 3.92)
Constipation	0%	2%	N/A
Diarrhoea	1%	3%	0.35 (0.05 to 2.38)
Nausea	3%	3%	1.04 (0.25 to 4.43)
Stomatitis	0%	0%	N/A
Vomiting	9%	5%	1.67 (0.60 to 4.71)
Hematological and lymphatic systems			
Anaemia	1%	1%	1.04 (0.11 to 9.91)
Leukopenia	6%	5%	1.04 (0.33 to 3.27)
Musculoskeletal system			
Arthralgia	9%	4%	2.09 (0.69 to 6.35)
Myalgia	7%	6%	1.04 (0.37 to 2.97)
Nervous system			
Parathesia	2%	1%	2.09 (0.28 to 15.79)
Respiratory tract			
Increased coughing	0%	1%	N/A
Dyspnea not related to heart failure	1%	1%	1.04 (0.11 to 9.91)
Pharyngitis	0%	2%	N/A
Skin			
Alopecia	26%	26%	1.00 (0.62 to 1.61)
Rash	1%	1%	1.04 (0.11 to 9.91)

For the assessment of cardiac-related adverse events an independent, blinded Cardiac Review and Evaluation Committee (CREC) was formed post hoc to review all cases of known or suspected cardiac dysfunction. The committee was composed of two oncologists and one cardiologist.⁶⁵

Table 17:
Commercial in confidence information removed from table.

A retrospective analysis of the cardiac events was performed as requested by the European Authority during the European Application procedure, the results of which were only presented according to the subgroup analysis of the specific chemotherapy regimen used (see table 18).

Table 18: Overview of cardiac events incidence

Classification of event according to likely aetiology	Study H0648g					
	T+P n/N (%)	P n/N (%)	p-value (χ^2)	T+AC n/N (%)	AC n/N (%)	p-value (χ^2)
Symptomatic heart failure 'anthracycline typical' (a)	7/91 (7.7%)	4/95 4.2%	0.314	35/143 (24.5%)	10/135 (7.4%)	<0.001
Definitive cardiac diagnosis other than heart failure (b)	4/91 (4.4%)	7/95 (7.4%)	0.390	8/143 (5.6%)	8/135 (5.9%)	0.906

T trastuzumab, P paclitaxel, AC anthracycline chemotherapy.

Categories are mutually exclusive.

- a) preferred terms: congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung oedema or other search terms and CRF information indicating cardiac failure (e.g. a combination of shortness of breath, dyspnoea, cough increase, pulmonary congestion on X-ray, echo or MUGA findings)
- b) cardiac condition most likely not related to adriamycin-typical heart failure (e.g. pericardial tamponade, syncope, stroke, angina pectoris, myocardial ischaemia, myocardial infarction, ascites)

Incidence of CREC diagnosed cardiac dysfunction

There was no significant difference in terms of cardiac events between those treated with paclitaxel alone and those who received paclitaxel plus trastuzumab. However, the addition of trastuzumab to anthracycline-based chemotherapy appears to increase the incidence of cardiac dysfunction in these patients.

Quality of life

Health related quality of life (HRQL) was assessed using the EORTC QLQ-C30 (version 1.0) with the breast cancer module (BR-23) at baseline, and at week 8, 20, and 32. Five prospectively defined domains (physical, role, social, global quality of life and fatigue) were regarded as primary. All remaining domains were secondary (pain, nausea/vomiting, cognitive, emotional, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, body image, sexual functioning, sexual enjoyment, future perspective, arm symptoms, breast symptoms, systemic therapy side effects and upset by hair loss). Data were analysed via repeated measures ANOVA using the last observation carried forward (death was assigned a value of '0'). Missing data at week 8 or 10 were not included in the analysis.

At baseline, 431 of 469 (92%) participants completed the questionnaire. At subsequent time points, the numbers of regularly scheduled questionnaires completed were 360 of 390 (95%) at week 8, 282 of 320 (88%) at week 20, and 160 of 181 (88%) at week 32.³⁰ By week 32, there were trends for improvement in all five primary as well as secondary domains. None of the differences in the primary domains reached statistical significance. However, significant differences were found in the pain domain and dyspnoea question of the QLQ-C30 and the systemic therapy side effects domain of the BR-23, all favouring the trastuzumab plus chemotherapy.³¹ The results may have been influenced by the fact that the analysis used the 'last observation carried forward' method. In patients with progressive disease, this approach tends to overestimate the results at the missing time points, since the scores from the completions at earlier time points in the study, before disease progression, are likely to be better (i.e., higher functioning scores and lower symptom scores) than those from later time points at which data are more likely to be missing.³⁰

Table 19: Quality of life for trastuzumab plus chemotherapy

Outcome	Trastuzumab Baseline Mean (\pm SE) (n=207)	Trastuzumab Week 32 Mean (\pm SE) (n=207)	Control Baseline Mean (\pm SE) (n=194)	Control Week 32 Mean (\pm SE) (n=194)
Global QoL	59.3 \pm 1.8	1.2 \pm 2.0	58.4 \pm 1.8	-3.9 \pm 2.0
Physical function	71.5 \pm 1.9	-2.9 \pm 2.1	70.6 \pm 2.1	-8.0 \pm 2.3
Social function	68.0 \pm 2.1	0.9 \pm 2.2	68.1 \pm 2.2	-4.5 \pm 2.4
Role function	64.6 \pm 2.5	-3.2 \pm 2.8	66.2 \pm 2.7	-9.3 \pm 2.9
Fatigue	37.6 \pm 1.9	1.1 \pm 2.2	36.9 \pm 2.0	6.7 \pm 2.1

A negative number indicates worsening for global QL, physical, role and social functioning, and an improvement for fatigue.

Incidence of CREC diagnosed cardiac dysfunction
Commercial in confidence information removed.

Monotherapy

Trastuzumab is currently licensed for the treatment of MBC overexpressing HER2 at the IHC level 3+. All three studies included women with MBC overexpressing HER2 at level 2+ and 3+. Where given, the results of the subseries analysis of women with tumours overexpressing HER2 at level 3+ is presented.

The duration of follow-up was not stated for one study.¹⁷ The median follow up in the remaining two studies included 12.8 months (range not given) in study H0649g²⁵ and 11 months (range 1.2 to 35 months) in study H0650g.²⁶

Response

The definitions used to measure response were presented for two studies (H0551g¹⁷ and H0649g).²⁵ Complete response was defined as the disappearance of radiographically, palpable, and/or visually apparent tumour. Partial response was defined as a \geq 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Disease progression was defined as a \geq 25% increase in any measurable lesion or the appearance of a new lesion.

All response outcomes (partial and complete) were measured by the investigators^{17, 25, 26} and confirmed by a blinded independent response evaluation committee (REC) in two studies ((H0551g¹⁷ and H0649g),²⁵ which was reported by Cobleigh et al to have been blinded.²⁵ The response rates reported in the current review includes those assessed according to the REC for two studies (H0551g¹⁷ and H0649g)²⁵ and according to the investigators for study H0650g.²⁶ Stable and progressive disease were assessed by the investigators in all three studies.

Table 20 summarises the data for response, and data on stable and progressive disease is presented in table 21.

The primary objective for all three studies was to measure overall response rate which ranged from 12% (study H0551g)¹⁷ to 24% (study H0650g, for participants randomised to the low dose group (LDG)).²⁶ Only two studies reported on the overall response rate for individuals with MBC overexpressing HER2 at level 3+, which ranged from 18% (study H0649g)²⁵ to 31% (study H0650g, for both treatment groups combined).²⁶ In other words, all participants who had an

overall tumour response in study H0650g had tumours that overexpressed HER2 at level 3+. This could also be said for the majority of tumour responses in study H0649g.

The number of participants who showed complete response ranged from 2% (study H0551g)¹⁷ to 7% (study H0650g, for participants randomised to the high dose group (HDG))²⁶ and partial response ranged from 9% (study H0551g)¹⁷ to 21% (study H0650g, for participants randomised to the LDG)²⁶ of participants. Only one study (H0649g) reported the number of participants with MBC overexpressing HER2 at level 3+ who showed complete or partial response, which included 5 (3%) and 26 (15%) respectively.²⁵

Table 20: Summary of tumour response for trastuzumab monotherapy

Study	All Participants	+3 HER overexpressors
Complete response (CR)		
<i>Study H0551g</i> ¹⁷	1/43 (2%)	
<i>Study H0649g</i> ²⁵	8/222 (4%)	5/172 (3%)
<i>Study H0650g</i> ²⁶ – LDG*	2/58 (3%)	
<i>Study H0650g</i> ²⁶ – HDG*	4/54 (7%)	
Partial response (PR)		
<i>Study H0551g</i> ¹⁷	4/43 (9%)	
<i>Study H0649g</i> ²⁵	26/222 (12%)	26/172 (15%)
<i>Study H0650g</i> ²⁶ – LDG*	12/58 (21%)	
<i>Study H0650g</i> ²⁶ – HDG*	8/54 (15%)	
Overall response		
<i>Study H0551g</i> ¹⁷	5/43 (11.6%, 95% CI: 4.36 to 25.9%)	
<i>Study H0649g</i> ²⁵	34/222 (15%, 95% CI: 11 to 21%)	31/172 (18%, 95% CI: 12.6 to 24.6%)
<i>Study H0650g</i> ²⁶ – LDG*	14/58 (24%, 95% CI: 13 to 35%)	26/85 (31%) (both groups combined)
<i>Study H0650g</i> ²⁶ – HDG*	12/54 (15%, 95% CI: 11 to 33%)	

*Study H0650g²⁶ was a RCT where participants were randomised to one of two treatment groups, within which trastuzumab was administered at a standard lower dose (LDG) or at a higher dose regimen (HDG).

The number of participants with stable disease was reported by all three studies and ranged from 4 (7%, for participants randomised to the LDG in study H0650g)²⁶ to 14 (33% for study H0551g).¹⁷ Disease progression was reported by two studies and was seen in 22 (51%, for study H0551g)¹⁷ and 93 (44%, for study H0649g)²⁵ participants. Neither stable disease or progressive disease was reported according to the level of HER2 overexpression in any study.

Table 21: Summary of stable and progressive disease for trastuzumab monotherapy

Outcome	Study H0551g¹⁷	Study H0649g²⁵	Study H0650g²⁶ – LDG*	Study H0650g²⁶ – HDG*
Stable disease	14/43 (33%)	62/222 (29%)	4/58 (7%) (stable disease at >6 months)	5/54 (9%) (stable disease at >6 months)
Disease progression	22/43 (51%)	93/222 (44%)		

*Study H0650g²⁶ was a RCT where participants were randomised to one of two treatment groups, within which trastuzumab was administered at a standard lower dose (LDG) or at a higher dose regimen (HDG).

Duration of response

The duration of response is presented in table 22. For study H0650g the data for the two intervention groups were only presented combined.²⁶

Two studies reported fairly similar duration of overall response and median time to disease progression (9.1 months and 3.1 months, respectively for study H0649g²⁵ and 9 months³⁴ and 3.4 months for study H0650g).²⁶

Median time to treatment failure, which was defined as the time from enrolment to disease progression, death, treatment discontinuation, or initiation of a new antitumour therapy was reported to be 2.4 months in study H0649g.²⁵ Study H0650g reported that for participants with an overall response, time to treatment failure was 8 months and for those with stable disease for more than 6 months it was 10.8 months.²⁶ The median time to progression of disease for participants, in study H0551g, with either minor (n=2) or stable disease (n=14) was 5.1 months.¹⁷

One study (H0649g) reported the median duration of response for participants whose tumours overexpress HER2 at level 3+, which included 9.1 months (range 5.6 to 10.3 months).²⁵ The same study reported that the median time to disease progression in this group was 3.2 months (range 2.6 to 3.5 months).

Table 22: Summary of duration of response (months) for trastuzumab monotherapy

Outcome	Study H0551g¹⁷	Study H0649g²⁵	*Study H0650g²⁶
Median duration of overall response (OR)		9.1 (range 1.6 to >26) (n=34) <i>HER2 overexpression at level 3+:</i> 9.1 (range 5.6 to 10.3) (n=172)	9 (n=16)
Median time to treatment failure		2.4 (range 0, to >28)	
Median time to disease progression		3.1 (range, 0 to >28) (n=213)	3.4 (n=113)
	<i>For participants with minor response or stable disease (SD)</i>	<i>HER2 overexpression at level 3+:</i> 3.2 (range 2.6 to 3.5)	<i>For participants with OR</i> 8

	5.1 (n=16)	(n=172)	(n=26) <i>For participants with SD at > 6 months 10.8</i>
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*Study H0650g²⁶ was a RCT where participants were randomised to receive trastuzumab at one of two dosage regimens. Data reported on duration of response was for both groups combined.

Survival

Survival data is presented in table 23.

Two studies reported data on survival end points (H0649g²⁵ and H0650g).²⁶ One study (H0649g) reported that the median survival time using Kaplan-Meier methodology was 13 months (range 0.5 to 30).²⁵ The same study reported that for participants with tumours overexpressing HER2 at level 3+ the median survival was 16.4 months. The median follow-up for this study was 12.8 months. For the second study (H0650g), 67% of participants were reported to be alive at a median follow-up of 11 months, with survival duration ranging from 1.2 to 35.3 months.²⁶

Table 23: Summary of survival (months) for trastuzumab monotherapy

Outcome	Study H0649g ²⁵	*Study H0650g ²⁶
Median duration of survival	13 (range 0.5 to 30) (n=222) <i>HER2 overexpression at level 3+: 16.4 (range 12.3 to 'upper limit not reached') (n=172)</i>	Range 1.2 to 35.3 (67% of participants)

*Study H0650g²⁶ was a RCT where participants were randomised to receive trastuzumab at one of two dosage regimens. Data reported on survival was for both groups combined.

Toxicity

The number of reported severe (grade 3 or 4) adverse events are presented in table 24. For one study (H0649g),²⁵ with the exception of data on laboratory abnormalities, this information represents adverse events that occurred in greater than 10% of the 213 participants who were treated with at least one dose of trastuzumab.

A blinded independent cardiac review and evaluation committee (CREC) was established retrospectively to assess cardiac dysfunction in all trastuzumab clinical trials.²⁵ An overview of the incidence of cardiac events reported by two studies (H0649g²⁵ and H0650g)²⁶ is presented in table 25.

Toxicity was minimal in study H0551g and no antibodies against the monoclonal antibody (rhuMAb HER2) were detected in any participant.¹⁷ Of the 768 administrations of trastuzumab, 11 events occurred that were considered to be related to treatment, ten of which were of moderate severity. Reported adverse events included fever and chills, pain at tumour site, diarrhoea, and nausea or vomiting. Three participants had cardiac dysfunction, two of whom died.³³

For study H0649g, the most common adverse events that were reported by approximately 40% of patients, were infusion-associated fever and/or chills that usually occurred only during the first infusion.²⁵ The most clinically significant adverse event was cardiac dysfunction, which occurred in ten patients (4.7%). Only 1% of patients discontinued the study because of treatment-related adverse events.

Adverse events for study H0650g were mainly mild to moderate in nature and occurred more frequently among participants treated with trastuzumab at a higher dose regimen.²⁶ Adverse events that are normally considered to be associated with chemotherapy were rare and included alopecia (n=4), anaemia (n=3), mucositis (n=1) and leucopenia (n=1). Only one participant had cardiac dysfunction (cardiac symptoms or asymptomatic decrease (>10%) in ejection fraction) according to the independent CREC.

Table 24: Severe adverse events (grade 3 or 4) for trastuzumab monotherapy

Outcome	Study H0551g¹⁷ n=46	Study H0649g²⁵ n=213	Study H0650g²⁶ – LDG* n=58	Study H0650g²⁶ – HDG* n=54
Any type				
Abdominal pain		4		
Asthenia		6	2	4
Back pain		1		
Chest pain		3		
Chills		5	0	1
Fever		2	1	0
Headache		4	1	1
Infection		1		
Pain	1	17		
Flu syndrome		1		
Pruritis		1		
Digestive tract				
Constipation		1		
Diarrhoea		3	1	3
Nausea		2		
Vomiting		1	1	2
Hematological and lymphatic systems				
Leukopenia		3		
neutropenia		2		
thrombocytopenia		2		
decreased hemoglobin		1		
Respiratory tract				
Increased coughing		1		
Dyspnea		10		
Hepatic laboratory abnormalities				
Elevated alkaline phosphatase		17		
AST		13		
ALT		5		

Total bilirubin		2		
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*Study H0650g²⁶ was a RCT where participants were randomised to one of two treatment groups, within which trastuzumab was administered at a standard lower dose (LDG) or at a higher dose regimen (HDG).

Table 25: Overview of the incidence of CREC diagnosed cardiac events for trastuzumab monotherapy

	<i>study H0649g²⁵</i>	<i>Study H0551g³³</i>	<i>Study H0650g²⁶</i>
Classification of event according to likely aetiology	Trastuzumab alone n=213/222	Trastuzumab alone n=46	Trastuzumab alone n=112/113
<i>Symptomatic heart failure 'anthracycline typical' (a)</i>	14 (6.6%)	3 cardiac dysfunction* (2 deaths due to cardiac dysfunction)	1 cardiac dysfunction* (likely aetiology not stated)
<i>Definitive cardiac diagnosis other than heart failure (b)</i>	5 (2.3%)		

Categories are mutually exclusive.

a) preferred terms: congestive heart failure, cardiomyopathy, heart failure, left ventricular failure, lung oedema or other search terms and CRF information indicating cardiac failure (e.g. a combination of shortness of breath, dyspnoea, cough increase, pulmonary congestion on X-ray, echo or MUGA findings)

b) cardiac condition most likely not related to adriamycin-typical heart failure (e.g. pericardial tamponade, syncope, stroke, angina pectoris, myocardial ischaemia, myocardial infarction, ascites)

*Cardiac dysfunction was manifested as congestive heart failure, cardiomyopathy, and/or a decrease in ejection fraction (>10%).

SUMMARY OF DATA ON THE EFFECTIVENESS OF TRASTUZUMAB

Combination therapy

The addition of trastuzumab to chemotherapy resulted in significantly less disease progression and treatment failure. The overall response was also found to be significantly greater in participants treated with trastuzumab plus chemotherapy compared to those in the chemotherapy alone treatment group. However, there was no significant difference between the two treatment groups for complete response.

Participants treated with trastuzumab plus chemotherapy had significantly longer progression free survival as well as overall survival than those treated with chemotherapy alone. Insufficient information was presented to calculate the hazard ratios for either outcome measure.

Commercial in confidence information removed from paragraph.

When looking at health related quality of life, there was no significant difference between the two groups with regard to any of the primary domains. However, it was reported that significant differences were found in the pain domain and dyspnoea question of the QLQ-C30 and the systemic therapy side effects domain of the BR-23, all favouring trastuzumab plus chemotherapy. The actual results were not presented.

Generally, trastuzumab used in combination therapy was well tolerated when compared to chemotherapy alone. There was no significant difference between trastuzumab plus chemotherapy and chemotherapy alone for almost all the most frequently reported serious adverse effects. There was however, a significantly greater incidence of congestive heart

failure reported among those treated with trastuzumab plus anthracycline-based chemotherapy but not amongst those receiving paclitaxel based chemotherapy.

In conclusion, trastuzumab when used in combination with chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) seems to be more effective than chemotherapy alone for the treatment of MBC over expressing HER2 at level 3+ in individuals who have not received prior treatment for MBC. However, it seems to be associated with an increased incidence of congestive heart failure when combined with anthracyclines.

Monotherapy

Trastuzumab, as monotherapy was shown to have some antitumour effects in terms of overall response (partial and complete) which according to three studied ranged from 12%¹⁷ to 24%²⁶. An independent response committee assessed response outcomes in two studies, which identified one (2%) complete response and four (9%) partial responses in one study (H0551g)¹⁷ and eight (4%) complete and 26 (12%) partial responses in the second (H0649g).²⁵ Response was assessed by the investigators in the third study (H0650g) which reported two (3%) complete and 12 (21%) partial responses among those treated in the low high dose group (HDG) and four (7%) complete and eight (15%) partial responses among participants in the high dose group (HDG).²⁶ Similar duration of response was reported by two studies ranging from 9 months (study H0650g)³⁴ to 9.1 months (study H0649g).²⁵

Only one study (H0649g) reported the number of complete or partial responses for participants with tumours overexpressing HER2 at level 3+, which included 5 (3%) and 26 (15%) respectively.²⁵ For study H0650g, the overall response rate for this group of participants was reported for both treatment groups combined and included 31% (26/85). These results show that the majority of tumour responses appeared in participants with tumours overexpressing HER2 at level 3+.

Two studies reported data on survival end points (H0649g²⁵ and H0650g).²⁶ One study (H0649g) reported that the overall median survival time using Kaplan-Meier methodology was 13 months (range 0.5 to 30), and that for participants with tumours overexpressing HER2 at level 3+ it was 16.4 months.²⁵ The median follow-up for this study was 12.8 months. For the second study (H0650g), 67% of participants were reported to be alive at a median follow-up of 11 months, with survival duration ranging from 1.2 to 35.3 months.²⁶

Trastuzumab when used as a single agent appears to have a relatively low toxicity level. The most common adverse events tended to be infusion related (e.g. fever and chills). The most clinically significant adverse event was cardiac toxicity.

There were no comparative studies of trastuzumab monotherapy, which means that there is uncertainty about the effectiveness of trastuzumab monotherapy, and therefore a RCT needs to be considered to fully establish whether it does more harm than good.

Table 26: Summary of the trastuzumab combination therapy findings

Study (n)	Type of therapy	Intervention details	Response	Survival	Quality of life	Adverse events
Trastuzumab as combination therapy						
Study H0648g^{8, 27-31} RCT (n=469)	1 st line	Trastuzumab plus chemotherapy versus chemotherapy alone. (Chemotherapy = anthracycline plus cyclophosphamide OR paclitaxel)	Progressive disease; treatment failure; overall response - significant differences in favour of trastuzumab. Complete response – no difference between groups.	Progression free survival – significantly greater in trastuzumab group. Overall survival – was significantly longer in trastuzumab group and of those who entered follow-up trial, significantly fewer deaths in trastuzumab group.	Significant differences in pain, dyspnoea and systemic therapy side effects favouring trastuzumab.	Significantly more congestive heart failure in trastuzumab group. No differences between groups for any other adverse events.

Table 27: Summary of the trastuzumab monotherapy findings

Study (n)	Type of therapy	Intervention details	Response	Duration of response	Survival	Adverse events
Trastuzumab as monotherapy						
Study H0551g¹⁷ Case series (n=46)	Not stated (82.6% had received prior chemo-therapy for MBC)	Trastuzumab at a loading dose of 250mg iv, then 10 weekly doses of 100mg.	Overall response: 12% (95% CI: 4 to 26), complete response: 2%, partial response: 9%			Toxicity was minimal.
Study H0649g^{25, 30} Case series (n=222)	2 nd or 3 rd line	Trastuzumab at a loading dose of 4mg/kg iv, followed by 2mg/kg maintenance dose at weekly intervals.	Overall response: 15% (95% CI: 11 to 21) (for HER 3+: 18%), complete response: 4% (for HER 3+:	Median duration of overall response: 9.1 months (range 1.6 to >26)	Median duration of survival was 13 months	The most common adverse events, which occurred in approximately 40% of participants, were

			3%), partial response: 12% (for HER 3+: 15%)			infusion-associated fever and/or chills that usually occurred during the first infusion, and were of mild to moderate severity. The most clinically significant adverse event was cardiac dysfunction, which occurred in 4.7 of participants.
Study H0650g ^{26, 38} RCT (trastuzumab given to both intervention groups as different regimens) (n=113: LDG n=58 and HDG n=54)	1 st line	Trastuzumab at a standard lower dose regimen (LDG): loading dose of 4mg/kg iv, followed by 2mg/kg maintenance dose at weekly intervals. <i>OR</i> Trastuzumab at a standard lower dose regimen (HDG): loading dose of 8mg/kg iv, followed by 4mg/kg maintenance dose at weekly intervals.	<i>LDG</i> Overall response: 24% (95% CI: 13 to 35), complete response: 3%, partial response: 21% <i>HDG</i> Overall response: 15% (95% CI: 11 to 33), complete response: 7%, partial response: 15% <i>HDG and LDG</i> , overall response for HER 3+: 31%	Median duration of overall response: 9 months	Survival ranged from 1.2 to >35.3 months	Adverse events were mainly mild to moderate, occurring more frequently in HDG. One participant had cardiac dysfunction.

3.3 ECONOMIC ANALYSIS

QUANTITY AND QUALITY OF ECONOMIC EVALUATIONS

INCLUDED STUDIES

Only one source of economic evaluations (which included two economic analyses) of trastuzumab was found to meet the inclusion criteria.⁸ The study was part of the industry submission data provided by Roche Ltd., and no economic evaluation was found via the literature searches.

The industry submission included a cost effectiveness analysis that compared the use of trastuzumab as a single agent with vinorelbine, and a cost utility and cost-effectiveness analysis of trastuzumab as part of a combination therapy (trastuzumab plus paclitaxel) compared with the single agent paclitaxel. Several important elements relating to the methods of both economic evaluations were classified as confidential.

The economic evaluation of trastuzumab as a single agent evaluated its use as second line therapy for MBC and trastuzumab as combination therapy was used as first line therapy for MBC. The economic study was based in the UK and was undertaken from the NHS perspective. The currency used was £ sterling and the cost year was 2000.

Trastuzumab as monotherapy

Source of effectiveness data

For the evaluation of trastuzumab as a monotherapy, the effectiveness data relating to trastuzumab was derived from a non-randomised study that included 222 women who had received prior chemotherapy for MBC (Roche study H0649g).⁸ Some supportive data were also derived from preliminary analysis of a study using trastuzumab as first line therapy for MBC (Roche study H0650g). Both studies are reported in the effectiveness section of this review. The data relating to vinorelbine was taken from a RCT (comparing vinorelbine with melphalan).⁷¹

Health outcomes

Clinical effectiveness of trastuzumab and vinorelbine as single agents were estimated using overall response rate (complete and partial) as determined by an independent and blinded response evaluation committee (REC) and the safety profile data, as primary endpoints. Secondary endpoints that were used included duration of response, 1-year survival, time to disease progression, time to treatment failure and quality of life scores (measured using the EORTC QLQ-C30). The health outcome used in the economic evaluation was median survival.

Measures of benefit

Benefit was measured in terms of life years gained (LYG).

Resource use

The resource data for both trastuzumab and vinorelbine were derived from the same studies as the clinical effectiveness data. The number of outpatient visits was assumed to be equal to the number of doses received. The resource use of adverse events was based on the number of participants hospitalised due to toxicity in the effectiveness trial.

Costs

Only direct medical costs were taken into account. Outpatient costs were based on Unit Costs of Health and Social Care PSSRU 1999, inflated to 2000 figures. Hospital cost for adverse events were based on assumptions made from a published study (no further details are given on how the cost was estimated). It was not stated how the actual costs of the drugs were derived but the prices used were reported. The time horizon used was 2 years.

Synthesis

The estimated costs and benefits were synthesised using incremental cost per life year gained.

Trastuzumab as combination therapy

Source of effectiveness data

For the evaluation of trastuzumab in combination with paclitaxel versus paclitaxel used as a single agent, the effectiveness data was derived from a single RCT which is included in the effectiveness section of the review (Roche study H0648g).²⁸

The trial included 469 participants. However, only a subset of these participants were included in the economic evaluation, i.e. only those who had received paclitaxel chemotherapy (n=188/469), and had MBC overexpressing HER2 at level 3+ (n=349/469). It was not stated exactly how many were included in the economic evaluation.

For ethical reasons, all participants with confirmed disease progression in the effectiveness trial were entitled to enroll on the follow-on protocol (study H0659g) which meant that they could receive trastuzumab. Only participants that did not switch to receive trastuzumab upon progression were included in the analysis.

Health outcomes

Clinical effectiveness was assessed using time to disease progression as the primary endpoint. Secondary endpoints included response rate, duration of response, 1-year survival and quality of life. **Commercial in confidence information removed from paragraph.**

Measures of benefit

The measures of benefit used included life years gained (LYG) and quality adjusted life years gained (QALY). UK-specific utility estimates associated with the disease states were taken from a published study and the standard gamble technique was used to calculate utility scores. It was not stated who was used to measure utility scores. The assumption was made that the utility level associated with a health state such as stable disease is the same before and after treatment. **Commercial in confidence information removed from paragraph.**

Resource use

The type of resource use taken into account included drug costs, outpatient costs (Unit costs of Health and Social Care PSSRU 1999), and adverse events costs. The costs of treatment infusion-related events however, were not included.

Costs

The economic analysis was based on a health state transition model which calculates the time participants stay within different health states. Utilities and direct medical costs associated with health states were used, together with clinical efficacy data. **Commercial in confidence information removed from paragraph.**

For trastuzumab used in combination with paclitaxel the economic evaluation included UK costs for the time spent in each health state used in the model, which were based on published

estimates. Standard costs were applied from national databases, published literature and hospital specific data. Drug costs were taken from MIMS, October 2000 and the cost of treating cardiac dysfunction was taken from a published study.⁷² **Commercial in confidence information removed from paragraph.**

QUALITY OF INCLUDED TRASTUZUMAB ECONOMIC EVALUATIONS

An overall summary of the quality of the included economic evaluations of trastuzumab is shown in table 31.

Study Question

The viewpoint of the analysis was considered to be clearly stated and justified for both trastuzumab as a monotherapy and as combination therapy.

Selection of alternatives

The comparators used for both trastuzumab as a monotherapy or combination therapy were clearly justified and detailed information relating to them were available in the referenced papers.

Form of evaluation

For the use of trastuzumab as combination therapy both a cost effectiveness and cost utility analysis were undertaken, which was deemed to be appropriate. For the evaluation of trastuzumab as a monotherapy, only a cost effectiveness analysis was undertaken, for which benefit was measured using LYG. Bearing in mind the poor prognoses of heavily pre-treated patients with MBC, using QALY as a measurement of benefit may have been more appropriate.

Effectiveness data

The source of effectiveness data for the use of trastuzumab as both monotherapy and combination therapy was clearly stated. The effectiveness data for trastuzumab as combination therapy was based on a single RCT. The effectiveness data for trastuzumab as monotherapy versus vinorelbine was based on two separate studies which means that a head to head comparison has not been undertaken. The study of trastuzumab as a single agent was a non-randomised study whereas the study relating to vinorelbine was a RCT, which means that there may be differences in the quality of the two trials affecting the comparability of the two treatment cohorts.

Benefit measurement and valuation

The primary outcome measures used for the economic evaluation of trastuzumab as a single agent and trastuzumab in combination therapy were clearly stated. The methods used to value states for trastuzumab as combination therapy was clearly referenced, although very little information is provided with regards to the type of individuals used to measure the utilities. Information relating to the participants for whom the survival data was based on is presented.

For trastuzumab used as monotherapy the measure of benefit (LYG) was based on the comparison of median survival, with trastuzumab being 16.4 months and vinorelbine 8.1 months i.e. median survival being twice as long in people given trastuzumab as compared to vinorelbine. There has been no head to head comparison of trastuzumab and vinorelbine and the data was derived from two separate cohorts. No baseline characteristics relating to the two cohorts were presented and the results relating to median survival were not explored in a sensitivity analysis despite the large difference in survival between the drugs.

For trastuzumab as a combination therapy, the RCT on which the economic evaluation is based included 469 participants, of whom only 188 received paclitaxel. Of these, only participants who had MBC overexpressing HER2 at level 3+ were included in the economic evaluation. Furthermore, 75% of participants who were randomised to receive paclitaxel alone switched to trastuzumab plus paclitaxel on disease progression, and only the remaining 25% were included in the economic evaluation. Heavy assumptions will therefore have been made about the survival data. **Commercial in confidence information removed from paragraph.**

Costing

The quantities of resources with regard to the drugs being used and outpatient visits were stated for both economic evaluations that evaluated the use of trastuzumab as a single agent or combination therapy. However, specific quantities of resources used with regard to adverse events were not stated. Both economic evaluations included information on methods used for estimating the quantities and unit costs, as well as the currency and price data. The relevancy of productivity changes was not reported for either economic evaluation.

Unlike vinorelbine and paclitaxel, trastuzumab is only indicated for MBC overexpressing HER2 at level 3+. However, no account seems to have been taken of the cost of HER2 testing for trastuzumab in either of the included economic evaluations. Nevertheless, recently published guidelines recommend that all individuals with MBC should be tested for HER2 status.¹³

Modelling

The details of the model used were reported for the economic evaluation of trastuzumab used as combination therapy. The choice of the parameters used were also justified. For trastuzumab used as a monotherapy it was stated that direct medical costs to the NHS were used and information is provided on what is costed and where the resource data is from, but resource quantities were not provided.

Adjustment for timing of costs and benefits

The time horizon used for both economic evaluation was clearly stated. For trastuzumab used as a combination therapy the discount rate was both stated and justified. For trastuzumab used as a monotherapy, the time horizon used was 2 years and therefore discounting was not needed.

Allowances for uncertainty

For trastuzumab used as combination therapy, details of statistical tests and confidence intervals were given for stochastic data. In addition, the choice of variables used in the sensitivity analysis was justified and the ranges over which they were varied were reported. The key parameters that were subjected to sensitivity analysis included time horizon, costs, utilities and efficacy rates.⁸ The two time horizons chosen were 5 years for the base case and zero years as a sensitivity analysis. The base case cost per QALY were most sensitive to utility weights assumptions, and the cost effectiveness ratios were quite sensitive to the time horizon of the survival extrapolation.

The overall median survival data used in the economic evaluation of trastuzumab combination therapy was based on a sub-population of participants included in the RCT (those relevant to the licensed indication). This sub set of participants included those who had received paclitaxel, with or without trastuzumab for the treatment of MBC overexpressing HER3 at level 3+ and did not cross over to the follow-on study (H0659g). When considering this sub-population of patients, who did not switch to trastuzumab on disease progression, the addition of trastuzumab to paclitaxel resulted in an increase in the median survival of 17.9 months (6.2 months for

paclitaxel alone and 24.1 months for trastuzumab plus paclitaxel). However, when considering all HER2 3+ participants who received paclitaxel, the survival advantage resulting from the addition of trastuzumab was 7 months (median survival was 18 months for paclitaxel alone and 25 months for trastuzumab plus paclitaxel). This large difference in the overall median survival advantage when only including participants who did not cross over to the follow-on study (H0659g) was not explored in the sensitivity analysis.

The only sensitivity analysis undertaken for trastuzumab as monotherapy was to compare the results with the cost effectiveness analysis using mitomycin as an alternative comparator which was reported to have the same survival data as vinorelbine. The approach used (e.g. multivariate) was not stated.

For trastuzumab as monotherapy, benefit was measured in terms of LYG. The median survival for trastuzumab was reported to be double that of vinorelbine (16.4 months versus 8.1 months, respectively). But other outcome measures such as median time to disease progression did not show trastuzumab to be so superior to vinorelbine (3.2 months versus 3 months⁷¹ respectively). A sensitivity analysis using variation in the assumptions and estimates underlying the analysis would have been useful.

Overall evaluation of quality

Overall the economic evaluation of trastuzumab as combination therapy was relatively well conducted. The viewpoint was clearly stated and justified, as was the choice of comparators. The choice of economic evaluation was appropriate. The effectiveness data was derived from a RCT. However, this information was taken from only a small sub set of participants included in the RCT, i.e. those relevant to the licensed indication (trastuzumab used in combination with a taxane for first line treatment for MBC overexpressing HER3 at level 3+). The RCT on which the data was derived included 469 participants, of whom only 188 received paclitaxel. Of these, only participants who had MBC overexpressing HER2 at level 3+ were included in the economic evaluation. Furthermore, 75% of participants who were randomised to receive paclitaxel alone switched to trastuzumab on disease progression and only the remaining 25% were included in the economic evaluation (having received trastuzumab as first line therapy only). When considering this sub-population of patients, who did not switch to trastuzumab on disease progression, the addition of trastuzumab to paclitaxel resulted in an increase in overall median survival of 17.9 months (6.2 months for paclitaxel alone and 24.1 months for trastuzumab plus paclitaxel). However, when considering all HER2 3+ participants who received paclitaxel, the survival advantage resulting from the addition of trastuzumab was 7 months (median survival was 18 months for paclitaxel alone and 25 months for trastuzumab plus paclitaxel). Although limiting the analyses to the licensed group of patients seems justified, this large difference in the overall median survival advantage when only including participants who did not cross over to the follow-on study (H0659g) should have been explored in the sensitivity analysis. Heavy assumptions will have been made about the survival data. However, two time horizons were chosen for the planned sensitivity analysis, 5 years for the base case and zero years for the sensitivity analysis. The cost effectiveness ratios were found to be quite sensitive to the time horizon of the survival extrapolation. **Commercial in confidence information removed from paragraph.**

The economic evaluation of trastuzumab as monotherapy was not considered to be as good. The viewpoint was clearly stated and justified, as was the choice of comparators. It was not clear why a CUA was not used. It was felt that a CEA that measured benefit using LYG only may not have been as preferable for heavily pre-treated patients with MBC. The sensitivity analysis was rather limited and the uncertainties around the data could have been explored

more. The effectiveness data for the two drugs was derived from separate studies which means that a head to head comparison was not undertaken. There has not been a randomised comparison to show that patients treated with trastuzumab have double the median survival of patients treated with vinorelbine. Data relating to trastuzumab was taken from a non-randomised study whilst the data for vinorelbine was derived from a RCT. The validity of the two studies would therefore, probably vary. The costs taken into account were reported but no information was provided on how these were calculated. Benefit was measured and valued correctly. A variation in the benefit data could have been further explored in the sensitivity analysis. However, the cost analysis is of limited validity as is the effectiveness evidence it is based on.

Table 28: Quality checklist for the economic evaluations of Trastuzumab

	<i>Roche Ltd., 2000⁸</i>	<i>Roche Ltd., 2000⁸</i>
Quality check list	<i>Monotherapy</i>	<i>Combination therapy</i>
<i>Study Question</i>		
The viewpoint(s) of the analysis are clearly stated and justified (e.g. provider, institution, societal)	✓	✓
<i>Selection of alternatives</i>		
Relevant alternatives are compared	✓	✓
The alternatives been compared are clearly described	✓	✓
The rationale for choosing the alternative programmes or interventions compared is stated	✓	✓
<i>Form of evaluation</i>		
The choice of form of economic evaluation is justified in relation to the question addressed	✓/✗	✓
<i>Effectiveness data</i>		
The source(s) of effectiveness estimates used are stated (e.g. single study, review, delphi panel)	✓	✓
Grade of evidence using those developed by members of the NHS R&D Centre for Evidence Based Medicine ⁷³ (see Appendix 5)	B	A
Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	NA	✓
<i>Benefit measurement and valuation</i>		
The primary outcome measure(s) for the economic evaluation are clearly stated (i.e. cases detected, life years, QALY's, willingness to pay etc.)	✓	✓
Methods to value states and other benefits are stated (e.g. time trade off, standard gamble)	NA	✓
Details of individuals from whom valuations were obtained are given	✓	✓
<i>Costing</i>		
Quantities of resources are reported separately from their unit costs (e.g. days on hospital)	✓/✗	✓/✗
Methods for estimation of quantities are described	✓	✓
The relevance of productivity changes to the study question is discussed	✗	✗

Productivity changes (if included) are reported separately	NA	NA
Currency and price date are reported	✓	✓
Details of currency of price adjustments for inflation or currency conversion are given	NA	NA
Modelling		
Details of any model used are given (i.e. decisions tree model, epidemiology model, regression model etc)	✓/✗	✓
The choice of model used and the key parameters on which it is based are justified	✓	✓
Adjustments for timing of costs and benefits		
Time horizon of costs and benefits is stated	✓	✓
The discount rate(s) is stated	NA	✓
The choice of rate is justified	NA	✓
A convincing explanation is given if cost or benefits are not discounted	NA	NA
Allowance for uncertainty		
Details of statistical tests and confidence intervals are given for stochastic data	✗	✓
The approach to sensitivity analysis is given (i.e. multivariate, univariate, threshold analysis etc)	✗	✗
The choice of variables for sensitivity analysis is justified	✗	✓
The ranges over which the variables are varied are stated	NA	✓
Presentation of results		
Incremental analysis is reported	✓	✓
Major outcomes are presented in disaggregated and aggregated form	✓	NA
Applicable to the NHS setting	✓	✓

✓ = Yes; ✗ = No; ✓/✗ = Partially covered; ? = not stated, not enough information or unclear; NA= not appropriate.

ASSESSMENT OF COST-EFFECTIVENESS

Trastuzumab as monotherapy

Clinical benefit

The median survival for trastuzumab was 16.4 months and the median survival for vinorelbine was 8.1 months.

Costs

The overall drug costs for trastuzumab were £5,296 and £1191 for vinorelbine. The NHS outpatient costs for trastuzumab were £900 compared to £600 for vinorelbine. The cost for the management of adverse events for trastuzumab were £0 and £22 for vinorelbine.

The total cost per patient for trastuzumab as monotherapy was £6,196 compared to £1,812 for vinorelbine.

Overall findings of economic evaluation of trastuzumab as monotherapy

Trastuzumab as monotherapy for second line treatment of MBC was found to be more effective but also more costly than vinorelbine (Matrix score A) and therefore an incremental analysis is required to aid decision-making.

CEA for monotherapy treatment with trastuzumab versus vinorelbine showed an incremental cost per LYG of £6,337.30. This ratio was driven by the significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

For the update review, Roche submitted further information on the economic model.⁷⁴ When the cost of cardiac assessment (£640) and IHC testing (£179) were taken into account the incremental cost per LYG ratio increased to £7,521.

Trastuzumab as combination therapy

Clinical benefit

Commercial in confidence information removed.

Costs

Commercial in confidence information removed.

The total cost for trastuzumab in combination with paclitaxel was £28,600, and the total cost for paclitaxel alone was £10,900.

Overall findings of economic evaluation of trastuzumab as combination therapy

Trastuzumab used in combination therapy with paclitaxel for first line therapy for MBC was found to be more effective but also more costly than paclitaxel used alone (Matrix score A) and therefore an incremental analysis is required to aid decision-making.

CEA for trastuzumab in combination with paclitaxel versus paclitaxel alone showed that the incremental cost per LYG for trastuzumab was £13,400 with an associated cost per QALY of £28,200. This may be an underestimation when considering the patients included in the effectiveness part of the economic analysis (see overall evaluation of quality).

For the update review, Roche submitted further information on the economic model.⁷⁴ When the cost of cardiac assessment (£640) and IHC testing (£179) were taken into account the incremental cost per LYG ratio increased to £14,069 and the cost per QALY increased to £29,448.

COST IMPLICATIONS OF TRASTUZUMAB TO THE NHS

According to the industry submission data, the overall budget impact of trastuzumab is £15.8 million which was derived from a model.⁸ The model took into account the licensed indication for trastuzumab and also included the cost of testing all patients with MBC for HER2 overexpression (calculated as £600,000). The assumptions made in the model were considered to be reasonable.

4. DISCUSSION

4.1 MAIN RESULTS

Effectiveness data

Combination therapy

There was only one included trial of trastuzumab plus chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone. The study population included women with overexpressing HER2 MBC at level 2+ or 3+ who had not received prior treatment for MBC. The median duration of follow-up was 30 months (range 30 to 51 months). The overall quality of the included trial was considered to be good.

The addition of trastuzumab to chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) resulted in significantly less disease progression and treatment failure and greater overall response when compared to chemotherapy alone. However, there was no significant difference between the two treatment groups for complete response. Participants treated with trastuzumab plus chemotherapy had significantly longer progression free survival than those treated with chemotherapy alone. There was a significantly greater incidence of congestive heart failure reported among those treated with trastuzumab plus anthracycline based chemotherapy compared to those on anthracycline alone. **Commercial in confidence information removed from paragraph.**

Monotherapy

Three studies looked at the use of trastuzumab as a single agent, none of which compared the use of trastuzumab with that of an alternative systemic therapy. The results should therefore, be interpreted with caution due to the possible influence of confounding factors. Two studies were caseseries (H0649g,²⁵ n=222 and H0551g,¹⁷ n=46) and one study (H0650g) was an RCT (n=113) that randomised participants to receive trastuzumab at a standard low dosage regimen (LDG) or at a higher dosage level (HDG).²⁶

All three studies included women with progressive MBC with HER2 overexpression at level 2+ or 3+, the majority of whom had received previous chemotherapy treatment, which was reported to have included an anthracycline or a taxane in two studies (H0649g²⁵ and H0650g).²⁶ The primary outcome measure for all three studies was overall response. The median follow-up was only reported in two studies and ranged from 11 months (H0650g)²⁶ to 12.8 months (H0649g).²⁵ The duration of follow up was considered to be sufficient to demonstrate an estimated response associated with trastuzumab, but may not have been long enough to assess long term patient response or survival, although prognosis is generally poor in patients with MBC. However, the reported median survival for patients with HER2 positive MBC is 9 to 12 months.⁸

The overall quality of the three studies was considered to be moderate according to the quality checklist for case-series. However, the RCT was considered to be of poor quality when using the check list for RCTs.

The three studies differed with many respects and therefore, the results may not be comparable. One study included women who had received extensive prior treatment for MBC (H0649g),²⁵ whilst a second study (H0650g)²⁶ used trastuzumab as first line therapy for MBC. The final study did not report the type of therapy that was used.¹⁷ The dosage regimen used in study H0551g¹⁷ and one of the treatment arms (high dosage regimen group) in study H0650g²⁶

differed to that which is currently used in clinical practice. An independent review committee assessed the response outcomes in two studies, (H0649g²⁵ and H0551g),¹⁷ which was reported to have been blinded according to Cobleigh et al.²⁵ In the third study the outcomes were assessed by the investigator.²⁶ For study H0649g, the number of participants that were deemed to have partial response according to the committee was lower than that reported by the investigators.²⁵

Trastuzumab, as monotherapy was shown to have some antitumour effects in terms of overall response (partial and complete) which ranged from 12% (H0551g)¹⁷ to 24% (H0650g).²⁶ Complete response ranged from 2% (study H0551g)¹⁷ to 7% (study H0650g, HDG)²⁶ and partial response ranged from 9% (H0551g)¹⁷ to 21% (H0650g, LDG).²⁶ Duration of response was reported by two studies ranging from 9 months (study H0650g)³⁴ to 9.1 months (study H0649g).²⁵

Only one study (H0649g) reported the number of complete or partial responses for participants with MBC overexpressing HER2 at level 3+, which included 5 (3%) and 26 (15%) respectively.²⁵ For study H0650g, the overall response rate for tumours overexpressing HER2 at level 3+ was reported for both treatment groups combined and included 31% (26/85). This means that the majority of responses were in tumours that overexpressed HER2 at level 3+.

Two studies reported data on survival end points (H0649g²⁵ and H0650g).²⁶ One study (H0649g) reported that the median survival time using Kaplan-Meier methodology was 13 months (range 0.5 to 30).²⁵ The median survival for participants with tumours overexpressing HER2 at level 3+ was 16.4 months. The median follow-up for this study was 12.8 months. For the second study (H0650g), 67% of participants were reported to be alive at a median follow-up of 11 months, with survival duration ranging from 1.2 to 35.3 months.²⁶

Trastuzumab when used as a single agent appears to have a relatively low toxicity level.

Economic data

The industry submission data included two economic evaluations.⁸ One evaluated trastuzumab as combination therapy with paclitaxel versus paclitaxel alone and one evaluated trastuzumab as monotherapy versus vinorelbine. For the update review, further information on the economic model was submitted by Roche, which included the overall impact of cardiac assessment costs and the IHC test costs.⁷⁴

Combination therapy

The economic evaluation of trastuzumab as combination therapy was relatively well conducted. Trastuzumab plus paclitaxel for first line therapy for MBC was found to be more effective but also more costly than paclitaxel used alone (Matrix score A). CEA for trastuzumab in combination with paclitaxel versus paclitaxel alone showed that the incremental cost per LYG for trastuzumab was £13,400 with an associated cost per QALY of £28,200. However, it is important to note that the data on survival was extrapolated from survival curves that only included participants who did not switch to trastuzumab on disease progression, all of whom had very poor prognosis and died during the trial.

When the overall cost of cardiac assessment (£640) and IHC testing (£179) is taken into account the incremental cost per LYG ratio was £14,069 and the cost per QALY was £29,448.

Monotherapy

The economic evaluation of trastuzumab as monotherapy was not considered to be as good and the cost analysis is of limited validity as is the effectiveness evidence it is based on. Trastuzumab for second line treatment of MBC was found to be more effective but also more costly than vinorelbine (Matrix score A). CEA for trastuzumab versus vinorelbine showed an incremental cost per LYG of £6337.30. This ratio was driven by the significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

When the overall cost of cardiac assessment and IHC testing is taken into account the incremental cost per LYG ratio was £7,521.

Overall findings

Overall, trastuzumab plus chemotherapy appears to be both effective (in terms of disease progression, treatment failure and overall response) and cost effective when used as second-line therapy for HER2 overexpressing MBC at level 3+ when compared to chemotherapy alone. However, there was no significant difference between the two treatment groups for complete response and it seems to be associated with congestive heart failure when combined with anthracycline based chemotherapy.

Trastuzumab, monotherapy appears to have some antitumour effects in terms of overall response (partial and complete) which according to three studies ranged from 12% (H0551g)¹⁷ to 24% (H0650g).²⁶ The median follow-up ranged from 11 months (H0650g)²⁶ to 12.8 months (H0649g).²⁵ Only 2 studies reported data on overall response for participants with tumours overexpressing HER2 at level 3+ and only one study reported using trastuzumab as second or third line therapy. No included study compared the use of trastuzumab with an alternative systemic therapy and the findings may therefore be subject to bias.

When compared to vinorelbine, trastuzumab monotherapy for second line therapy for MBC was found to have a matrix score of A and an incremental cost effectiveness ratio of £7,521 per LYG. However, this ratio was driven by an assumed significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

Budget impact of trastuzumab to the NHS

According to data provided within the industry submission the budget impact for trastuzumab is £15.8 million.⁸

4.2 ASSUMPTIONS, LIMITATIONS AND UNCERTAINTIES

Effectiveness data

For the evaluation of trastuzumab monotherapy, none of the included studies compared the use of trastuzumab with that of an alternative systemic therapy, which means that the results of these studies should be interpreted with caution. When investigating the use of an intervention, it is important to consider that the observed effect may not necessarily be due to the therapeutic intervention itself. It is possible that it could have occurred by chance, or alternatively, represent variability of disease status, or due to some other confounding factor. Confounding factors can produce bias (the systematic deviation of a measurement from the 'true' value)⁷⁵ and include extraneous factors (e.g. lifestyle, the use of other medication, placebo effect), the natural course of the disease (the influence of different prognostic factors) and information errors (incorrect

assessment or reporting of the outcome measure). Using a well conducted double blind RCT means that these confounding factors are controlled for, providing an un-biased estimate of the effect. In other words, the observed effect will either be due to the intervention or chance (random variation). Random variations can be minimised by using a large enough sample size. Observational studies, on the other hand, may yield estimates of association that may deviate from true underlying relationships beyond the play of chance.²² However, it is acknowledged that undertaking a RCT of trastuzumab used as second line or third line therapy may be problematic due to the lack of proven therapy available to use as a control. However, the effectiveness of trastuzumab is also not yet proven which means a RCT of trastuzumab monotherapy versus no therapy may be justified.

The randomisation procedure was performed and reported adequately in the trastuzumab trial (according to the industry submission data). Proper randomisation ensures that selection bias (systematic differences between comparison groups in prognosis or responsiveness to treatment) is avoided by ensuring that participants have a prespecified (very often equal) chance of being assigned to the experimental or control group. An adequate procedure for generating a random number list should therefore be used.⁷⁵ Concealment of treatment allocation was also thought to have been adequate in the trastuzumab trial. Fore-knowledge of group assignments leaves the allocation sequence subject to manipulation by researchers and participants.⁷⁵ Concealed random allocation of interventions by an independent person who is not responsible for determining the eligibility of patients is therefore essential. Previous research has demonstrated that randomised and non-randomised controlled trials may produce different results.⁷⁶ RCTs that have used an inadequate randomisation procedure or have not clearly demonstrated allocation concealment may overestimate the treatment effect size.⁷⁶

For the RCT of trastuzumab combination therapy (study H0648g)¹⁶ and one case series of trastuzumab monotherapy (study H0649g),²⁵ the primary outcome measure and the incidence of congestive heart failure was assessed by an independent committee that was blinded to treatment group assignment. However, other outcomes were assessed by the investigators who were not reported to have been blinded to treatment group assignment. None of the included studies reported blinding of the administrators or participants (to having received trastuzumab). Whilst blinding in cancer trials is acknowledged to be difficult to undertake due to the nature of the disease and of the drugs being given, blinding is important in that it avoids observer bias and is therefore essential for any subjective clinician evaluating outcome measures such as alleviation of symptoms and QOL. Previous research has shown that non-blinded studies can overestimate the treatment effect.⁷⁷ Non-blindness of administrators can result in biased administration of co-interventions.

It is important in any trial that baseline characteristics are comparable between intervention groups. The most important baseline characteristics, as determined by the expert panel for this review, were not all reported on for the trastuzumab combination trial or studies of monotherapy. It cannot therefore, be assumed that the participants in each treatment group did not differ with respect to these factors.

The trastuzumab combination trial included women with overexpressing HER2 MBC at level +2 and +3. For all outcome measures, the participants with HER2 overexpressing MBC at level 3+ were not compared to those with level 2+ but all participants, which included those with HER2 level 3+. As the majority of participants were HER2 level 3+ (349/469) which dominated the total group, it is not possible to draw conclusions about patients with level 2+ for outcome measures. **Commercial in confidence information removed from paragraph.**

When reporting a RCT with survival-type data the recommended appropriate summary statistics that should be used are the log hazard ratio and its variance.⁷⁸ For the trastuzumab combination therapy trial no hazard ratio or measure of its variance were reported. However, the analysis relating to median survival and duration of response, for the trial and one case series of trastuzumab monotherapy, were reported to have been based on Kaplan-Meier methodology, which means that the time to event was explicitly considered for each individual in the study.²² For the RCT only the P value of the log rank test was reported along with the median time, and for the case series only the median time was given.

Response to treatment is a surrogate outcome measure for assessing the effects of treatment on survival or quality of life. Because women with MBC have such poor prognosis, tumour shrinkage may alleviate symptoms (especially pain) and improve quality of life, which means that information relating to complete or partial response would be important but not independent from quality of life. However, alleviation of symptoms was not addressed by most included studies, which is surprising as these outcomes are probably the most important for this patient group. Therefore, as partial response is a surrogate measure for complete response, conclusions about effectiveness should be drawn from the complete response findings. Conclusions should not be drawn on the findings of partial response when used as a surrogate measure, unless outcomes relating to symptom relief are also reported or the results of both partial and complete response are in the same direction.

The likelihood of a single trial to produce false positive results is considerably higher than that of two consecutive trials.⁷⁹ As only one trial was included for the review of combination therapy, the findings of ongoing trials will be very important in the next few years.

The presence of publication bias, especially concerning the review of observational studies can not be ruled out. Studies that do not show the intervention to be effective or do not report significant findings are not always published, which can result in publication bias. This may be due to the reluctance of the authors themselves or due to the editorial policies of journals. This can be a particular problem with industry sponsored studies with companies often only wanting to publish positive results relating to their products, or alternatively there may be a longer delay in publication of less positive findings.

Cost-effectiveness data

It is important that where possible the data on the effectiveness for different interventions used in economic evaluations is derived from the same controlled trial, otherwise the effectiveness of the intervention can not be assured. The economic evaluation that looked at the cost effectiveness of trastuzumab monotherapy versus vinorelbine did not include a head to head comparison for the effectiveness data. This means that the two study populations, used to assess the effectiveness of each intervention, may have differed with regards to prognosis or responsiveness to treatment (selection bias).

To undertake an economic evaluation a comparator is needed. As there are no comparative studies of trastuzumab monotherapy the effectiveness data should be derived from a systematic review of an alternative therapy. For the included economic evaluation of trastuzumab monotherapy, vinorelbine was used as the comparator. However, the effectiveness data was taken from a single RCT of vinorelbine versus melphalan,⁷¹ whilst the effectiveness of trastuzumab monotherapy was taken from a non-comparative phase II study (H0649g).²⁵ Ideally the vinorelbine effectiveness data should be based on a systematic review which includes phase II data. If however, vinorelbine is not considered to be an appropriate

comparator then a systematic review of follow-up data where participants received no further treatment for advanced MBC should be used.

For both cost effectiveness analyses the measure of benefit was dependent on survival, which was extrapolated from short-term analyses and no allowance was made for uncertainty. It is very important that these assumptions and uncertainties are explored in sensitivity analyses, which were limited in both included economic evaluations.

4.3 NEED FOR FURTHER RESEARCH

Further large well-conducted RCTs are required to investigate trastuzumab in the settings for which it is currently indicated (in the treatment of HER2 overexpressing MBC at level 3+). Such trials should include sufficient numbers of participants to answer the research question. Randomisation procedures (including allocation concealment) should be adequate and clearly reported, as should the duration of the treatment. Outcome assessments should be blind where possible. Baseline characteristics of participants should be reported (including data on distribution) and any discrepancies should be controlled for in the analysis. The length of follow-up should be long enough to ensure adequate assessment of response and survival data. Outcomes assessed should include alleviation of symptoms and pain. The number of people in the control group who received the treatment under investigation on disease progression should also be clearly reported. When reporting survival data, the log hazard ratio and its variance should be presented.

Further research is needed to evaluate the optimum duration of therapy as well as less inconvenient schedules than weekly infusions. Indefinite weekly treatment not only has resource implications, but will also affect the patient. Roche are currently undertaking a phase II study to investigate the pharmacokinetics and safety of trastuzumab and paclitaxel administered together as a three weekly regimen in the treatment of MBC.⁸⁰ Preliminary information from ongoing studies suggests that the half-life of trastuzumab is now approximately 25 days rather than 5-6 days indicated by earlier studies.^{80, 81} A large NHS funded trial is required to show whether a three-weekly regimen is equivocal to a weekly regimen in terms of efficacy. **Commercial in confidence information removed from paragraph.**

Further cost effectiveness research

Although the use of trastuzumab as combination therapy for MBC looks promising, further trials are required to evaluate its cost-effectiveness in patients overexpressing HER2 at level +3 including all patients in the economic analysis for which the drug is currently indicated.

Further cost-effectiveness analysis should be undertaken at the same time as future RCTs of trastuzumab (used in the setting indicated for use in the UK) where data on cost and effectiveness is collected simultaneously. It may also be plausible to undertake a RCT that includes a direct comparison of trastuzumab and vinorelbine (which includes stratification according to the HER2 level of participants) which will provide more accurate effectiveness data for the cost-effectiveness analysis. The trial should also take into account the cost of HER2 testing that is necessary for the use of trastuzumab and should also allow for the comparison of the adverse effects profile of the two therapies.

5. CONCLUSIONS

Trastuzumab when used in combination with chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) seems to be more effective than chemotherapy alone for the treatment of MBC overexpressing HER2 at level 3+ in individuals who have not received prior treatment for MBC. However, it seems to be associated with congestive heart failure when given in combination with anthracyclines. **Commercial in confidence information removed from paragraph.**

When compared to paclitaxel, trastuzumab used in combination therapy with paclitaxel for first line therapy for MBC was found to have a matrix score of A (higher costs but better outcomes) and an incremental cost effectiveness ratio of £14,069 LYG and £29,448 per QALY.

Trastuzumab monotherapy when used as second line or subsequent therapy for the treatment of MBC overexpressing HER2 at level 3+ appears to have some antitumour effects in terms of overall response (partial and complete). It also appears to have a relatively low toxicity level. No included study compared the use of trastuzumab with an alternative systemic therapy or no/standard treatment and the findings may therefore be subject to bias. Without better effectiveness data, it is difficult to adequately assess the cost effectiveness of trastuzumab monotherapy.

When compared to vinorelbine, trastuzumab monotherapy for second line therapy for MBC was found to have a matrix score of A and an incremental cost effectiveness ratio of £7,521 per LYG. However, this ratio was driven by an assumed significant survival advantage of trastuzumab over vinorelbine, which was not derived from a randomised comparison or explored in a sensitivity analysis.

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APPENDICES

APPENDIX 1: SEARCHES

INITIAL SEARCH

Scoping Search

A rapid appraisal to identify ongoing and completed systematic reviews was undertaken on the 3rd June 2000. The rapid appraisal search process involved searching a checklist of resources for the drug names (trastuzumab/Herceptin) and breast cancer.

Main Literature Search

The following databases and Internet sites were searched:

MEDLINE: Silverplatter. CD-ROM. 1986-2000/08.

The searches were carried out on 5th September 2000 and identified 48 records.

EMBASE: Silverplatter. CD-ROM . 1989-2000/07.

The searches were carried out on 5th September 2000 and identified 101 records.

Cancerlit: Silverplatter. CD-ROM . 1995-2000/06.

The searches were carried out on 7th September 2000 and identified 31 records.

BIOSIS-Web: Edina. Internet. 1993-2000.

The searches were carried out on 7th September 2000 and identified 75 records.

Index to Scientific and Technical Proceedings (ISTP): Web of Science. Internet. 1990-2000.

The searches were carried out on 11th September 2000 and identified 10 records.

Cochrane Controlled Trials Register (CCTR): Cochrane Library, 2000:3. CD-ROM.

The searches were carried out on 6th September 2000 and identified 3 records.

National Research Register (NRR): 2000:3. CD-ROM.

The searches were carried out on 12th September 2000 and identified 4 ongoing and 6 complete trials.

UKCCCR Register

This site was searched on the 14th September 2000 and identified 0 trials.

National Institute of Health

This site was searched on the 14th September 2000 and identified 20 trials.

Current Controlled Trials (CCT)

This site was searched on the 14th September 2000 and identified 8 trials.

CenterWatch Clinical Trials Listing Service

This site was searched on the 14th September 2000 and identified 2 trials.

National Cancer Institute

This site was searched on the 14th September 2000 and identified 19 trials.

American Society of Clinical Oncology (ASCO)

This site was searched on the 14th September 2000 and identified 10 ASCO Abstracts on trastuzumab/Herceptin.

MEDLINE: Silverplatter. CD-ROM. 1986-2000/08. 5th September 2000.

The search strategy was designed to find randomised controlled trials and cost effectiveness studies and therefore used relevant methodological filters. Breast cancer terms and the drug names (trastuzumab/Herceptin) were then added to the quality filters. The MEDLINE searches covered the date range 1986 to August 2000. The searches were carried out on 5th September 2000 and identified 48 records.

```
#1 randomized controlled trial in pt
#2 explode "randomized controlled trials"/all subheadings
#3 "random allocation"/all subheadings
#4 "double blind method"/ all subheadings
#5 "single blind method"/ all subheadings
#6 clinical trial in pt
#7 explode "clinical trials"/all subheadings
#8 "controlled clinical trials"/ all subheadings
#9 (clin* near3 trial*) in ti, ab
#10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*))in ti,ab
#11 placebo* in ti,ab
#12 "placebos"/all subheadings
#13 random* in ti,ab
#14 explode "research design"/all subheadings
#15 explode "Evaluation-Studies"/ all subheadings
#16 "Follow-Up-Studies"/ all subheadings
#17 "Prospective-Studies" / all subheadings
#18 (control* or prospectiv* or volunteer*) in ti,ab
#19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or
#15 or #16 or #17 or #18
#20 tg=animal
#21 tg=human
#22 #20 not (#20 and #21)
#23 #19 not #22
#24 explode "economics"/ all subheadings
#25 (cost or costs or costed or costly or costing) in ti,ab
#26 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
#27 #25 near #26
#28 (economic* or pharmacoeconomic* or price* or pricing) in ti,ab
#29 #24 or #27 or #28
#30 #23 or #29
#31 explode "breast neoplasms"/all subheadings
#32 (breast* near4 (cancer* or tumo?* or malignant*)) in ti,ab
#33 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#34 #31 or #32 or #33
#35 (herceptin or haerceptin) in ti,ab,nm
#36 trastuzumab in ti,ab
#37 #35 or #36
```

#38 #34 and #37
#39 #30 and #38

EMBASE: Silverplatter. CD-ROM . 1989-2000/07. 5th September 2000.

The MEDLINE search strategy above was translated and adapted to run in the EMBASE database. The EMBASE searches covered the date range 1989 to July 2000. The searches were carried out on 5th September 2000 and identified 101 records.

#1 "randomized-controlled-trial"/ all subheadings
#2 "randomization"/ all subheadings
#3 "double-blind-procedure"/ all subheadings
#4 "single-blind-procedure"/ all subheadings
#5 (random* near control* trial*) in ti,ab
#6 (clin* near3 trial*) in ti,ab
#7 explode "clinical trial"/ all subheadings
#8 explode "controlled study"/ all subheadings
#9 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*)) in ti,ab
#10 placebo* in ti,ab
#11 "placebo"/ all subheadings
#12 "evaluation"/ all subheadings
#13 "follow up"/ all subheadings
#14 "prospective study"/ all subheadings
#15 (control* or prospective* or volunteer*) in ti,ab
#16 random* in ti,ab
#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 (explode "animal"/ all subheadings) or (explode "animal experiment"/ all subheadings)
#19 (explode "human"/ all subheadings) or (explode "human experiment"/ all subheadings)
#20 #18 not (#18 and #19)
#21 #17 not #20
#22 explode "economics"/ all subheadings
#23 explode "health economics"/ all subheadings
#24 (cost or costs or costed or costly or costing) in ti, ab
#25 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
#26 #24 near #25
#27 #22 or #23 or #26
#28 #21 or #27
#29 explode "breast-cancer"/ all subheadings
#30 (breast* near4 (cancer* or tumo?* or malignant*)) in ti,ab
#31 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
#32 #29 or #30 or #31
#33 (herceptin or haerceptin) in ti,ab,tn
#34 "trastuzumab"/ all subheadings
#35 trastuzumab in ti,ab
#36 #33 or #34 or #35
#37 #32 and #36
#38 #28 and #37

Cancerlit: Silverplatter. CD-ROM . 1995-2000/06. 7th September 2000.

The MEDLINE search strategy above was translated and adapted to run in the Cancerlit database. The Cancerlit searches covered the date range 1995 to June 2000. The searches were carried out on 7th September 2000 and identified 31 records.

- #1 randomized controlled trial in pt
- #2 explode "randomized controlled trials"/all subheadings
- #3 "random allocation"/all subheadings
- #4 "double blind method"/ all subheadings
- #5 "single blind method"/ all subheadings
- #6 clinical trial in pt
- #7 explode "clinical trials"/all subheadings
- #8 "controlled clinical trials"/ all subheadings
- #9 (clin* near3 trial*) in ti, ab
- #10 ((singl* or doubl* or trebl* or tripl*) near3 (blind* or mask*))in ti,ab
- #11 placebo* in ti,ab
- #12 "placebos"/all subheadings
- #13 random* in ti,ab
- #14 explode "research design"/all subheadings
- #15 explode "Evaluation-Studies"/ all subheadings
- #16 "Follow-Up-Studies"/ all subheadings
- #17 "Prospective-Studies" / all subheadings
- #18 (control* or prospectiv* or volunteer*) in ti,ab
- #19 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
or #15 or #16 or #17 or #18
- #20 explode "economics"/ all subheadings
- #21 (cost or costs or costed or costly or costing) in ti,ab
- #22 (utilit* or benefit* or effective* or stud* or minimi* or analys*) in ti,ab
- #23 #21 near #22
- #24 (economic* or pharmacoeconomic* or price* or pricing) in ti,ab
- #25 #20 or #23 or #24
- #26 #19 or #25
- #27 explode "breast neoplasms"/all subheadings
- #28 (breast* near4 (cancer* or tumo?* or malignant*)) in ti,ab
- #29 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
- #30 #27 or #28 or #29
- #31 (herceptin or haerceptin) in ti,ab,nm
- #32 trastuzumab in ti,ab
- #33 #31 or #32
- #34 #30 and #33
- #35 #26 and #34

BIOSIS-Web: Edina. Internet. 1993-2000. 7th September 2000.

<http://edina.ed.ac.uk/biosis/>

BIOSIS-Web was searched via Edina on the Internet. As this interface only accepts simple search strategies the randomised controlled trials and cost effectiveness studies filters were not used. A simple search strategy using the drug names (trastuzumab/Herceptin) and breast

cancer terms was used. The resulting references were then deduplicated against those records already found. The BIOSIS-Web searches covered the date range 1993 to 2000. The searches were carried out on 7th September 2000 and identified 75 records.

(herceptin or trastuzumab) and breast*

Index to Scientific and Technical Proceedings (ISTP): Web of Science. 1990-2000. Internet. 11th September 2000. <http://wos.mimas.ac.uk/>

The Web of Science interface used to search Index to Scientific and Technical Proceedings (ISTP) only accepts simple search strategies, so the randomised controlled trials and cost effectiveness filters were not used. A simple search combining the drug names and breast cancer terms was implemented. The ISTP searches covered the date range 1990 to 2000. The searches were carried out on 11th September 2000 and identified 10 records.

Cochrane Controlled Trials Register: Cochrane Library, 2000:3. CD-ROM. 6th September 2000.

The Cochrane Controlled Trials Register (CCTR) was searched to find completed trials. A relatively simple search was used, combining the drug names with terms for breast cancer. The search strategy did not require methodological filters for randomised controlled trials because the database only consists of controlled trial references. The searches were carried out on 6th September 2000 and identified 3 records.

- #1 BREAST-NEOPLASMS*:ME
- #2 (BREAST* AND (((CANCER*) or TUMOUR*) OR TUMOUR*) OR MALIGNANT*))
- #3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
- #4 ((#1 or #2) or #3)
- #5 (HERCEPTIN or HAERCEPTIN)
- #6 TRASTUZUMAB
- #7 (#5 or #6)
- #8 (#4 and #7)

National Research Register: CD-Rom, 2000:3. CD-ROM. 12th September 2000.

The National Research Register (NRR) was searched to find further ongoing and completed trials. A relatively simple search strategy was used, combining the drug names and terms for breast cancer. The searches were carried out on 12th September 2000 and identified 4 ongoing and 6 complete trials.

- #1 BREAST-NEOPLASMS*:ME
- #2 (BREAST* AND (((CANCER*) or TUMOUR*) OR TUMOUR*) OR MALIGNANT*))
- #3 (BREAST* AND ((ONCOLOG*) or CARCINOMA*))
- #4 ((#1 or #2) or #3)
- #5 (HERCEPTIN or HAERCEPTIN)
- #6 TRASTUZUMAB

- #7 (#5 or #6)
#8 (#4 and #7)

Internet Resources.

A number of Internet sites were chosen to search for information about further ongoing trials. The sites included the main trials registers; UKCCCR Register, National Institute of Health, Current Controlled Trials (CCT) and CenterWatch Clinical Trials Listing Service. The trials register of the National Cancer Institute was also searched (Cancernet). In addition the American Society of Clinical Oncology (ASCO) website was searched for abstracts from their annual conference proceedings.

The search strategy for all of the Internet sites consisted of the drug terms only. The results were then browsed to find references dealing with breast cancer only.

TRASTUZUMAB

HERCEPTIN

UKCCCR Register

http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html

This site was searched on the 14th September 2000 and identified 0 trials.

National Institute of Health

<http://clinicaltrials.gov/ct/gui/c/r>

This site was searched on the 14th September 2000 and identified 20 trials.

Current Controlled Trials (CCT)

http://www.controlled-trials.com/login.cfm?returnto=home_page.cfm

This site was searched on the 14th September 2000 and identified 8 trials.

CenterWatch Clinical Trials Listing Service

<http://www.centerwatch.com/main.htm>

This site was searched on the 14th September 2000 and identified 2 trials.

National Cancer Institute

<http://cancernet.nci.nih.gov/trialsrch.shtml>

This site was searched on the 14th September 2000 and identified 19 trials.

American Society of Clinical Oncology (ASCO)

<http://www.asco.org/>

This site was searched on the 14th September 2000 and identified 10 ASCO Abstracts on Trastuzumab/Herceptin. Abstracts that had already been found in the previous database searches were discounted.

The search results from MEDLINE, EMBASE, Cancerlit, BIOSIS-Web, Index to Scientific and Technical Proceedings and the Cochrane Controlled Trails Register were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted.

The search results from the National Research Register were downloaded in full into a text file.

The search results from the Internet were saved as HTML files.

UPDATE SEARCH

An update search was undertaken in order to find more information about Phase II studies. It was decided to rerun the original searches without the RCT and economic evaluation methodological search filters. Methodological filters were not used in the original searches for the Biosis, Index to Scientific and Technical Proceedings (ISTP), Cochrane Controlled Trials Register (CCTR) and the National Research Register (NRR) databases, so remained exactly the same.

Main Literature Search

The following databases were searched:

MEDLINE
EMBASE
Cancerlit
BIOSIS-web
Index to Scientific and Technical Proceedings (ISTP)
Cochrane Controlled Trails Register (CCTR)
National Research Register (NRR)

MEDLINE: Silverplatter. CD-ROM. 1986-2001/05. 13th August 2001.

The search strategy was designed to find all studies and was therefore kept very simple for sensitive results. Breast cancer terms and the drug names (Herceptin/Trastuzumab) were combined in the search strategy. The MEDLINE search covered the date range 1986 to May 2001. The search was carried out on 13th August 2001 and identified 119 records.

#1 (herceptin or haerceptin) in ti,ab,nm
#2 trastuzumab in ti,ab,nm
#3 #1 or #2
#4 explode "Breast-Neoplasms"/ all subheadings
#5 (breast near4 (cancer* or tumo?* ot malignant*)) in ti,ab
#6 (breast near4 (oncolog* or carcinoma*)) in ti,ab
#7 #4 or #5 or #6
#8 #3 and #7
#9 tg=animal
#10 tg=human
#11 #9 not (#9 and #10)
#12 #8 not #11

EMBASE: Silverplatter. CD-ROM . 1989-2001/07. 13th August 2001.

The MEDLINE search strategy above was translated and adapted to run in the EMBASE database. The EMBASE search covered the date range 1989 to July 2001. The search was carried out on 13th August 2001 and identified 333 records.

- #1 (herceptin or haerceptin) in ti,ab,tn
- #2 "trastuzumab"/ all subheadings
- #3 trastuzumab in ti,ab,tn
- #4 #1 or #2 or #3
- #5 explode "breast-cancer"/ all subheadings
- #6 (breast* near4 (cancer* or tumo?* or malignant*)) in ti,ab
- #7 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
- #8 #5 or #6 or #7
- #9 #4 and #8
- #10 (explode "animal"/ all subheadings) or (explode "animal-experiment"/ all subheadings)
- #11 (explode "human"/ all subheadings) or (explode "human experiment"/ all subheadings)
- #12 #10 not (#10 and #11)
- #13 #9 not #12

Cancerlit: Silverplatter. CD-ROM . 1995-2001/03. 13th August 2001.

The MEDLINE search strategy above was translated and adapted to run in the Cancerlit database. The Cancerlit search covered the date range 1995 to March 2001. The search was carried out on 13th August 2001 and identified 87 records.

- #1 explode "breast neoplasms"/all subheadings
- #2 (breast* near4 (cancer* or tumo?* or malignant*)) in ti,ab
- #3 (breast* near4 (oncolog* or carcinoma*)) in ti,ab
- #4 #1 or #2 or #3
- #5 (herceptin or haerceptin) in ti,ab,nm
- #6 trastuzumab in ti,ab,nm
- #7 #5 or #6
- #8 #4 and #7

**BIOSIS-Web: Edina. Internet. 1993-2001 (updated 2nd August 2001). 13th August 2001.
<http://edina.ed.ac.uk/biosis/>**

BIOSIS-Web was searched via Edina on the Internet. A simple search strategy using the drug names (Herceptin/Trastuzumab) and breast cancer terms was used. The resulting references were then deduplicated against those records already found. The BIOSIS-Web searches covered the date range 1993 to 2001. The search was carried out on 13th August 2001 and identified 204 records.

(herceptin or trastuzumab) and breast*

Index to Scientific and Technical Proceedings (ISTP): Web of Science. 1990-2001 (updated 10th August 2001). Internet. 13th August 2001. <http://wos.mimas.ac.uk/>

The Web of Science interface used to search Index to Scientific and Technical Proceedings (ISTP). A simple search combining the drug names and breast cancer terms was implemented. The ISTP search covered the date range 1990 to 2001. The search was carried out on 13th August 2001 and identified 17 records.

(herceptin or trastuzumab) and breast*

Cochrane Controlled Trials Register: Cochrane Library, 2001:3. CD-ROM. 13th August 2001.

The Cochrane Controlled Trials Register (CCTR) was searched to find completed trials. A relatively simple search was used, combining the drug names with terms for breast cancer. The searches were carried out on 13th August 2001 and identified 17 records.

- #1 BREAST-NEOPLASMS*:ME
- #2 (BREAST* AND (((CANCER* or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
- #3 (BREAST* AND ((ONCOLOG* or CARCINOMA*))
- #4 ((#1 or #2) or #3)
- #5 (HERCEPTIN or HAERCEPTIN)
- #6 TRASTUZUMAB
- #7 (#5 or #6)
- #8 (#4 and #7)

National Research Register: CD-Rom, 2001:2. CD-ROM. 13th August 2001.

The National Research Register (NRR) was searched to find further ongoing and completed trials. A relatively simple search strategy was used, combining the drug names and terms for breast cancer. The searches were carried out on 13th September 2001 and identified 3 ongoing and 10 complete trials

- #1 BREAST-NEOPLASMS*:ME
- #2 (BREAST* AND (((CANCER* or TUMOR*) OR TUMOUR*) OR MALIGNANT*))
- #3 (BREAST* AND ((ONCOLOG* or CARCINOMA*))
- #4 ((#1 or #2) or #3)
- #5 (HERCEPTIN or HAERCEPTIN)
- #6 TRASTUZUMAB
- #7 (#5 or #6)
- #8 (#4 and #7)

The search results from MEDLINE, EMBASE, Cancerlit, BIOSIS-Web, Index to Scientific and Technical Proceedings and the Cochrane Controlled Trails Register were downloaded and imported into Endnote (ISI ReSearchSoft, USA) reference management software and duplicate records were deleted.

The search results from the National Research Register were downloaded in full into a text file.

APPENDIX 2: EXCLUDED STUDIES

LIST OF EXCLUDED STUDIES FROM INITIAL SEARCHES

To be included in the initial review, studies had to fulfil all of the following criteria:

1. The study design must be an RCT or a full economic evaluation (cost effectiveness/cost–minimisation analysis, cost-utility analysis or cost-benefit analysis).
2. The study must evaluate trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) alone or in combination with other agents versus systemic therapy without trastuzumab.
3. The study must include individuals with breast cancer.
4. The study must include one of the following outcome measures: response (including complete and partial response); progression free survival; overall survival; symptom relief; quality of life; adverse effects; or costs.

Study	Study design	Intervention	Population	Comments
Alegre et al., 1994 ⁸²	x	x	✓	Not trastuzumab, not a RCT.
Anon, 1998 ³⁹	x	✓	✓	Non-systematic review
Baselga, 1999 ³¹	x	✓	✓	Analysing safety data taken from three trials
Beuzeboc et al., 1999 ⁴⁰	x	✓	✓	Non-systematic review
Burriss et al., 1999 ⁴⁴	x	✓	✓	No comparison group (docetaxel in combination with trastuzumab)
Burriss et al., 1999 ⁴⁵	x	✓	✓	No comparison group (docetaxel in combination with trastuzumab)
Burstein et al., 1999 ⁴⁶	x	✓	✓	No comparison group (trastuzumab in combination with vinorelbine)
Chia et al., 2000 ⁴⁹	x	✓	x	Laboratory based data, not human participants
Cobleigh et al., 1999 ²⁵	x	✓	✓	No comparison group (trastuzumab monotherapy, therefore included in update review)
Cobleigh, 1999 ³⁵	x	✓	✓	no comparison group (trastuzumab monotherapy, therefore included in update review)
Esteva et al., 1999 ⁴⁷	x	✓	✓	No comparison group (trastuzumab in combination with paclitaxel)
Feldman et al., 2000 ²⁰	x	✓	✓	Discussion data
Hortobagyi, 1999 ⁴¹	x	x	✓	Review of docetaxel
Konecny et al., 1999 ⁵⁰	x	✓	x	In cell lines, not patients
Luftner et al., 1999 ⁵¹	x	x	✓	Evaluation of changing levels of HER2 in patients treated with paclitaxel
McLachlan et al., 1999 ⁵²	x	x	✓	Not a drug trial
Pegram & Slamon, 1999 ⁴⁸	x	✓	✓	No comparison group (trastuzumab in combination with cisplatin)
Seidman et al., 1999 ¹⁸	x	✓	✓	No comparison group (trastuzumab in combination with paclitaxel)
Untch et al., 2000 ⁴³	x	✓	✓	Non-English language, non-systematic review
Wong et al., 1999 ⁴²	x	✓	✓	Non-systematic review

LIST OF EXCLUDED STUDIES FROM UPDATE SEARCHES

To be included in the update review, studies had to fulfil all of the following criteria:

1. The study design must be a cohort study, case control study or a case-series.
2. The study must evaluate trastuzumab (Herceptin®, Genentech, Inc., South San Francisco, California) used as a single agent.
3. The study must include individuals with breast cancer overexpressing HER2 at level 3+.
4. The study must include one of the following outcome measures: response (including complete and partial response); progression free survival; overall survival; symptom relief; quality of life; adverse effects; or costs.

Study	Study design	Intervention	Population	Comments
Baselga, 2000 ³³	x	✓	✓	Non-systematic review
Baselga, 2000 ⁵⁴	x	✓	✓	Non-systematic review
Fleming, 1999 ⁶⁵	x	✓	✓	Non-systematic review looking at the design of clinical trials
Kish et al., 2001 ⁶⁷				Comparison of serum and tissue HER2 overexpression in MBC prior to trastuzumab therapy.
Kute et al., 2000 ⁶⁸	x	✓	x	Studied the effect of trastuzumab on cellular DNA and cell cycle.
Heinzl, 2000 ⁶⁴	x	✓	✓	Non-systematic review
Hiddemann, 2001 ⁶¹	x	✓	✓	Review with no primary research
Horton, 2001 ⁵⁵	x	✓	✓	Non-systematic review
Norton et a., 1998 ⁵⁶	x	✓	✓	Non-systematic review
Perez Lopez et al., 2000 ⁵⁷	x	✓	✓	Non-systematic review
Pohlmann, 2000 ⁵⁸	x	✓	✓	Review with no primary research
Roche, 1999 ⁶⁶	x	x	✓	Tested a cohort of women with breast cancer for HER2 overexpression
Sparano, 2001 ⁵⁹	x	✓	✓	Non-systematic review on cardiac toxicity of trastuzumab
Tokuda et al., 1999 ⁵³	✓	✓	x	Phase I study of trastuzumab in patients with HER2 overexpressing MBC. Study was excluded because tumours were considered to overexpress HER2 if at least 10% of tumour cells had positive membrane staining (HER2 overexpression at level 2+ means that 25-50% of tumour cells have positive staining) ¹⁷ and the number of participants with HER2 overexpression at level 3+ was not reported.
Treish et al., 2000 ⁶⁰	x	✓	✓	Non-systematic review including data in HER2 testing
Wagner, 2000 ⁶³	x	✓	✓	Review with no primary research
Wagner, 2000 ⁶²	x	✓	✓	Review with no primary research

APPENDIX 3: STAGING OF BREAST CANCER
Simplified UICC staging of breast cancer⁸³

T (Tumour size)	T1	tumour less than 2cm
	T2	tumour 2-5 cm
	T3	tumour more than 5cm
	T4	tumour of any size fixed to skin or chest wall
N (Presence of axillary nodes)	N0	no palpable axillary lymph nodes
	N1	mobile ipsilateral nodes
	N2	fixed ipsilateral nodes
	N3	supraclavicular or infraclavicular nodes
M (Presence of metastases)	M0	no distant metastases
	M1	distant metastases

Combinations of these are used to define clinical staging. Early breast cancer is comprised of stages I and II; advanced of stages III and IV.

- Stage I** Small tumour (<2 cm)

- Stage II** Tumour >2cm but < 5cm, lymph nodes negative
or
Tumour <5cm, lymph nodes positive, no detectable distant metastases

- Stage III** Large tumour (>5cm)
or
Tumour of any size with invasion of skin or chest wall
or
Associated with positive lymph nodes in the supraclavicular region but no detectable distant metastases

- Stage IV** Tumour of any size
Lymph nodes either positive or negative
Distant metastases

APPENDIX 4: QUALITY CHECKLISTS

STUDIES OF CLINICAL EFFECTIVENESS

RCTs were assessed using the following criteria, based on CRD Report No. 4:⁷⁵

1. Was the method used to assign participants to the treatment groups really random?
(Computer generated random numbers and random number tables will be accepted as adequate, whilst inadequate approaches will include the use of alternation, case record numbers, birth dates or days of the week)
2. Was the allocation of treatment concealed?
(Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other methods with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque)
3. Was the number of participants who were randomised stated?
4. Were details of baseline comparability presented in terms of treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
5. Was baseline comparability achieved for treatment free interval, disease bulk, number of previous regimens, age, histology and performance status?
6. Were the eligibility criteria for study entry specified?
7. Were any co-interventions identified that may influence the outcomes for each group?
8. Were the outcome assessors blinded to the treatment allocation?
9. Were the individuals who were administered the intervention blinded to the treatment allocation?
10. Were the participants who received the intervention blinded to the treatment allocation?
11. Was the success of the blinding procedure assessed?
12. Were at least 80% of the participants originally included in the randomisation process, followed up in the final analysis?
13. Were the reasons for any withdrawals stated?
14. Was an intention to treat analysis included?

Cohort studies were assessed according to the following criteria, based on CRD Report No. 4:⁷⁵

1. Is there sufficient description of the groups and the distribution of prognostic factors?
2. Are the groups assembled at a similar point in their disease progression?
3. Is the intervention/treatment reliably ascertained?
4. Were the groups comparable on all important confounding factors?
5. Was there adequate adjustment for the effects of these confounding variables?
6. Was a dose-response relationship between intervention and outcome demonstrated?
7. Was outcome assessment blind to exposure status?
8. Was the follow-up long enough for the outcomes to occur?
9. What proportion of the cohort was followed-up?
10. Were drop-out rates and reasons for drop-out similar across intervention and unexposed groups?

Case-control studies will be assessed according to the following criteria, based on CRD Report No. 4:⁷⁵

1. Is the case definition explicit?

2. Has the disease state of the cases been reliably assessed and validated?
3. Were the controls randomly selected from the source of population of the cases?
4. How comparable are the cases and control with respect to potential confounding factors?
5. Were interventions and other exposures assessed in the same way for cases and control?
6. How was the response rate defined?
7. Were the non-response rates and reasons for non-response the same in both groups?
8. Is it possible that over-matching has occurred in that cases and controls were matched on factors related to exposure?
9. Was an appropriate statistical analysis used (matched or unmatched)?

Case series will be assessed according to the following criteria, based on CRD Report No. 4:⁷⁵

1. Is the study based on a representative sample selected from a relevant population?
2. Are the criteria for inclusion explicit?
3. Did all individuals enter the survey at a similar point in their disease progression?
4. Was the follow-up long enough for important events to occur?
5. Were outcomes assessed using objective criteria or was blinding used?
6. If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?

Items were graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/✗ partially (item partially addressed), ? unclear or not enough information, or **NA** not applicable.

STUDIES OF COST EFFECTIVENESS

Studies of cost effectiveness were assessed using the following criteria, based on the checklist developed by Drummond & Jefferson, 1996.⁸⁴

Study question

1. The viewpoint(s) of the analysis are clearly stated and justified
(*Provider institution, individual clinician, professional organisation, patient or patient group, purchaser or health care or society*)

Selection of alternatives

2. Relevant alternatives are compared
3. The alternatives being compared are clearly described
(*Who did what, to whom, where and how often*)
4. The rationale for choosing the alternative programmes or interventions compared is stated

Form of evaluation

5. The choice of form of economic evaluation is justified in relation to the questions addressed
(*Cost-benefit analysis – whether benefits are greater than costs for one intervention*
Cost minimisation analysis – if effects are equal what is less costly
Cost effectiveness analysis – if costs and effects vary
Cost utility analysis – best way to spend a given budget)

Effectiveness data

6. The source(s) of effectiveness estimates used are stated
(*Single study, selection of studies, systematic review, delphi panel*)

7. The source(s) of effectiveness estimates (*Grade of evidence using those developed by members of the NHS R&D Centre for Evidence Based Medicine*⁷³ i.e. A, B, C, or D see appendix 5)
8. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)

Benefit measurement and valuation

9. The primary outcome measure(s) for the economic evaluation are clearly stated (*Cases detected, life years, QALYs, willingness to pay etc*)
10. Methods to value health states and other benefits are stated (*Time trade off, standard gamble, willingness to pay, contingent valuation etc*)
11. Details of the individuals from whom valuations were obtained are given (*Patients, members of the public, health care professionals etc*)

Costing

12. Quantities of resources are reported separately from their unit costs (*Days in hospital etc*)
13. Methods for estimation of quantities are described
14. The relevance of productivity changes to the study question is discussed
15. Productivity changes (if included) are reported separately
16. Currency and price data are reported
17. Details of currency of price adjustments for inflation or currency conversion are given

Modelling

18. Details of any model used are given (*Decisions tree model, epidemiology model, regression model etc*)
19. The choice of model used and the key parameters on which it is based are justified

Adjustments for timing of costs and benefits

20. Time horizon of costs and benefits is stated
21. The discount rate(s) is stated
22. The choice of rate is justified
23. A convincing explanation is given if cost or benefits are not discounted

Allowance for uncertainty

24. Details of statistical tests and confidence intervals are given for stochastic data
25. The approach to sensitivity analysis is given (*Multivariate, univariate, threshold analysis etc*)
26. The choice of variables for sensitivity analysis is justified
27. The ranges over which the variables are varied are stated

Presentation of results

28. Incremental analysis is reported
29. Major outcomes are presented in a disaggregated as well as aggregated form
30. Applicable to the NHS setting

Items were graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/✗ partially (item partially addressed), ? unclear or not enough information, or **NA** not applicable.

APPENDIX 5: LEVELS OF EVIDENCE BASED ON THOSE DEVELOPED BY MEMBERS OF THE NHS R&D CENTRE FOR EVIDENCE-BASED MEDICINE (CHRIS BALL, DAVE SACKETT, BOB PHILLIPS, BRIAN HAYNES, AND SHARON STRAUS).⁷³

Grade	Level of Evidence	Therapy
A	1a	Systematic review (with homogeneity) of RCTs
	1b	Individual RCT (with Narrow Confidence Interval)
	1c	All or none§
B	2a	Systematic review (with homogeneity) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
	2c	"Outcomes" Research
	3a	Systematic review (with homogeneity) of case-control studies
	3b	Individual Case- Control Study
C	4	Case-series (and poor quality cohort and case-control studies§§)
D	5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

NOTES

§ Met when all patients died before the treatment became available, but some now survive on it; or when some patients died before the treatment became available, but none now die on it.

§§ By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

APPENDIX 6: TRASTUZUMAB COMBINATION THERAPY TRIAL

Study and design	Participants	Intervention details	Adverse effects/ withdrawals	Comments
<p>Slamon et al., 1999²⁸ (Data also extracted from Norton et al., 1999,⁶⁵ Slamon et al., 1998,²⁷ Baselga et al., 1999,⁶⁶ Osoba & Burchmore, 1999,³⁰ abstract published in the Oncologist, 1998⁶⁷ and company submission data by the pharmaceutical company Roche).⁸</p> <p>Study details: A multicentre randomised phase III trial (Roche Study H0648g)</p> <p>Method of randomisation: Commercial in confidence information removed. Randomisation was stratified by type of chemotherapy regimen that patients were receiving.</p> <p>Objective: To assess the efficacy of Herceptin® (trastuzumab) in combination with chemotherapy as first-line treatment for women with metastatic breast cancer overexpressing HER2.</p> <p>Length of follow-up: The last patient was enrolled on 7 March 1997³⁴. Commercial in confidence information removed from paragraph.</p> <p>The final analysis of the primary endpoints was performed 9 months after enrolment of the last patient. Survival was analysed 31 months after enrolment ended. The median duration of follow-up was 35 months (range 30 to 51).</p>	<p>Number of participants: 469. First participant was enrolled 12 June 1995 and the last participant was enrolled March 7 1997.</p> <p>Type of breast cancer: Metastatic breast cancer overexpressing HER2 (at a 2+/ 3+ level). 249/469 women had a tumour expressing HER at 3+ level.</p> <p>All patients had tumours that overexpressed HER2 as determined by immunohistochemistry (IHC)⁶⁵ Commercial in confidence information removed from paragraph.</p> <p>Age range: 25-77 years Mean age (yrs) (range): H+ AC = 54 (27-76); H+T = 51 (25-77) AC = 54 (25-75); T = 51 (26-73)</p> <p>Inclusions criteria: Metastatic breast cancer. Overexpression of the HER2 oncogene (2+ to 3+. Commercial in confidence information removed from paragraph. Ability to understand and willingness to give informed consent Commercial in confidence information removed from paragraph.</p> <p>Exclusion criteria: Commercial in confidence information removed from paragraph.</p> <p>Previous treatment: Prior adjuvant chemotherapy H+ AC = 57%; H+T = 97% AC = 37%; T = 100% Prior hormonal therapy: H+ AC = 142/143; H+T = 89/92 AC = 134/138; T = 95/96 Prior radiotherapy: H+ AC = 143/143; H+T = 89/92</p>	<p>Type of therapy: first line (no prior chemotherapy treatment for metastatic disease)</p> <p>Intervention: Chemotherapy and trastuzumab (CRx + H). Chemotherapy included either anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) or paclitaxel (T) (n=235) (AC + H; n = 143) (T + H; n = 92) Dosage: Trastuzumab: 4mg/kg loading, then 2mg/kg intravenously every week. Chemotherapy: Doxorubicin 60mg/m2 iv, epirubicin 75mg/m2 iv, cyclophosphamide 600mg/m2 iv, paclitaxel 175mg/m2 iv over 3 hours, given every 3 weeks No. of cycles: 6 for chemotherapy and trastuzumab for duration of trial.</p> <p>Comparator: Chemotherapy alone (CRx). Chemotherapy included either anthracycline (doxorubicin or epirubicin) plus cyclophosphamide (AC) or paclitaxel (T) (n=234) (AC; n= 138) (T; n = 96) Dosage: Doxorubicin 60mg/m2 iv, epirubicin 75mg/m2 iv, cyclophosphamide 600mg/m2 iv, paclitaxel 175mg/m2 iv every 3 hours, given over 3 weeks No. of cycles: 6</p> <p>Further information: All women received chemotherapy prior to randomisation (to H therapy). Randomisation was stratified by type of</p>	<p>Commercial in confidence information removed from paragraph.</p> <p>Withdrawals: 5 randomised patients discontinued participation in the study before Day 1 (assigned to the chemotherapy regimen to which they were stratified for analysis) for the following reasons: death (n=1), investigator-determined disease progression (n=1); patient request (n=2); inadvertent enrolment (n=1).</p> <p>Commercial in confidence information removed from paragraph.</p> <p>Adverse effects: Trastuzumab was well tolerated except for Class III/IV cardiac dysfunction, more common with AC+H (19%) than T+H (4%).</p> <p>At a median follow-up of 10.5 months a syndrome of myocardial dysfunction similar to that observed with anthracyclines was reported more commonly with AC+H (18% Grade 3/4) than with AC alone (3%), T (0%), or T+H (2%) (Slamon, 1998⁸⁸)</p> <p>The reported incidence of any cardiac dysfunction (which could include dyspnea, increased cough, paroxysmal nocturnal dyspnea, peripheral edema, S3 gallop, and reduced ejection fraction) was 28% in patients treated with trastuzumab plus anthracycline and 7% in patients treated with anthracycline alone. Patients randomised to H+T had a reported 11% incidence of cardiac dysfunction, compared with 1% with T alone. 19% of patients in H+AC cohort developed congestive heart failure of class III or IV severity.⁶⁹</p> <p>Commercial in confidence information removed.</p>	<p>Author's conclusions: Addition of Herceptin to chemotherapy increased response rate and time-to-disease progression significantly compared with chemotherapy alone.</p> <p>Other comments: Many of the analyses and conclusions are based on subgroup analysis (dependent on type of chemotherapy patients received or level of HER overexpression).</p> <p>Many patients randomised to chemotherapy alone received subsequent trastuzumab alone or with other drugs which would skew the data for survival. Although overall survival was still superior with initial chemotherapy plus trastuzumab treatment.⁶⁷</p> <p>Changes to initial trial protocol:⁶⁵ More inclusive eligibility criteria (inclusion criteria broadened and requirement of histologically confirmed metastases removed)</p> <p>Simplified study procedures (less tests required and trastuzumab infusion time reduced)</p> <p>More flexible concomitant chemotherapy</p> <p>Elimination of placebo infusion</p>

<p>Responses to treatment were confirmed by an independent Response Evaluation Committee (REC) which was composed of independent oncologists and radiologists. The radiographs +/- or physical examination findings were evaluated in a blinded manner.⁶⁵ Commercial in confidence information removed from paragraph.</p> <p>Kaplan-Meier survival methodology was used to estimate the median time to disease progression for each treatment group. A two-sided log-rank test was used to compare the time to disease progression for the two treatment groups. The statistical analysis plan specified that disease progression be attributed only in the presence of radiographic evidence and/or death. A two-sided χ^2 test was used to compare the overall response rates between the two treatment groups. Kaplan-Meier survival methodology was used to estimate the median duration of response, median time to treatment failure, and median survival time for each treatment group. Two sided log-rank tests were used to compare the two treatment groups with respect to each of these secondary efficacy variables. Commercial in confidence information removed from paragraph.</p>	<p>AC = 136/138; T = 95/96 Commercial in confidence information removed from paragraph.</p> <p>Other baseline characteristics: 3+ HER2 overexpression: H+ AC = 76%; H+T = 74% AC = 70%; T = 80% Karnofsky score between 90-100/60-80 H+ AC = 66%/34%; H+T = 76%/24% AC = 66%/34%; T = 65%/35% Median number of +ve lymph nodes at diagnosis H+ AC = 1.0; H+T = 5.0 AC = 0.5; T = 6.0 ≥ 3 metastatic sites at enrolment: H+ AC = 40%; H+T = 31% AC = 29%; T = 35% Median disease-free interval (months): H+ AC = 24.5; H+T = 22.4 AC = 22.8; T = 18.9</p>	<p>chemotherapy regimen that patients were receiving, which included: AC in patients having received no prior anthracycline (A) containing chemotherapy (n=281) and paclitaxel to those who had previously received A therapy (n=188) in the adjuvant setting.</p> <p>For ethical reasons, at the time of disease progression patients were allowed to enrol into the follow-up protocol H0659g which permitted all patients to receive trastuzumab. 76% of HER 3+ sub group who were initially randomised to receive paclitaxel alone underwent a treatment switch to H.⁸</p> <p>Subgroup (% getting subsequent H) AC (57%, AC+H (32%), p (74%), H+T (43%).⁸⁵</p>		
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<p>Results</p> <p>Outcome 1: Median time to disease progression (months) (primary end point).</p> <p>Commercial in confidence information removed from paragraph.</p>	<p>Outcome 2: Treatment failure</p> <p>Time to treatment failure was defined conservatively as disease progression, death, treatment discontinuation for any other reason or initiation of new antitumour therapy.</p> <p>Commercial in confidence information removed from</p>	<p>Outcome 3: Median duration of response (months)</p> <p>Duration of major response (complete or partial response sustained for ≥ 4 weeks) was defined as the time from the initial complete or partial response to documented disease progression or death (whichever occurred first).</p> <p>Follow up time: Data cut-off point 31 December 1997 (minimum follow-up of</p>
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<p>Disease progression was defined as an increase of more than 25% in the dimensions of any measurable lesion.</p> <p>Analysed using Kaplan-Meier survival methodology and log-rank test.</p> <p>Follow up time: Data cut-off point 31 December 1997 (minimum follow-up of 9 months).</p> <p>For all participants (ITT)</p> <table border="0"> <tr><td>CRx+H</td><td>7.4 (95% CI 7.0 to 9.0)</td></tr> <tr><td>AC+H</td><td>7.8 (95% CI 7.3 to 9.4)</td></tr> <tr><td>T+H</td><td>6.9 (95% CI 5.3 to 9.9)</td></tr> </table> <table border="0"> <tr><td>CRx</td><td>4.6 (95% CI 4.4 to 5.4)</td></tr> <tr><td>AC</td><td>6.1(95% CI 4.9 to 7.1)</td></tr> <tr><td>T</td><td>2.7 (95% CI 2.1 to 4.3)</td></tr> </table> <p>Commercial in confidence information removed from paragraph.</p> <p>CRx+H vs CRx p=0.0001 AC+H vs AC p<0.05 T+H vs T p<0.05</p> <p>Commercial in confidence information removed from paragraph.</p> <p>For participants with HER2 3+ (n=349)</p> <table border="0"> <tr><td>CRx+H = 7.8</td><td>CRx = 4.6 (p<0.05)</td></tr> <tr><td>AC+H = 8.1</td><td>AC = 6.0 (p<0.05)</td></tr> <tr><td>T+H = 7.1</td><td>T = 3.0 (p<0.05)</td></tr> </table> <p>Commercial in confidence information removed from paragraph.</p>	CRx+H	7.4 (95% CI 7.0 to 9.0)	AC+H	7.8 (95% CI 7.3 to 9.4)	T+H	6.9 (95% CI 5.3 to 9.9)	CRx	4.6 (95% CI 4.4 to 5.4)	AC	6.1(95% CI 4.9 to 7.1)	T	2.7 (95% CI 2.1 to 4.3)	CRx+H = 7.8	CRx = 4.6 (p<0.05)	AC+H = 8.1	AC = 6.0 (p<0.05)	T+H = 7.1	T = 3.0 (p<0.05)	<p>paragraph.</p> <p>Median time to treatment failure (months) (evaluable participants)</p> <p>CRx+H = 6.9 (95% CI: 6.0 to 7.3) vs CRx = 4.5 (95% CI: 4.3 to 4.9) p=0.0001</p> <p>H+ AC = 7.2 (95% CI: 6.2 to 7.8) vs AC = 5.6 (95% CI: 4.6 to 6.4) , p=0.0014</p> <p>H+T = 5.8 (95% CI: 4.4 to 7.1) vs T = 2.9 (95% CI: 2.0 to 4.3) p=0.0001</p>	<p>9 months). Patients were evaluated for response at week 8 and 20 and then at 12 week intervals.</p> <p>For all participants (ITT)</p> <p>CRx+H = 9.1 (95% CI 7.7 to 11.0) vs CRx = 6.1 (95% CI 5.5 to 7.8) p<0.05 H+ AC = 9.1 (95% CI 7.4 to 12.2) vs AC = 6.7 (95% CI 5.8 to 8.2) p<0.05 H+T = 10.5 (95% CI 7.3 to 12.5) vs T = 4.5 (95% CI 3.9 to 6.4) p<0.05</p> <p>Commercial in confidence information removed from paragraph.</p> <p>For participants with HER2 3+ (n=349)</p> <table border="0"> <tr><td>CRx+H = 10.0</td><td>CRx = 5.6</td></tr> <tr><td>AC+H = 9.3</td><td>AC = 5.9</td></tr> <tr><td>T+H = 10.9</td><td>T = 4.6</td></tr> </table>	CRx+H = 10.0	CRx = 5.6	AC+H = 9.3	AC = 5.9	T+H = 10.9	T = 4.6
CRx+H	7.4 (95% CI 7.0 to 9.0)																									
AC+H	7.8 (95% CI 7.3 to 9.4)																									
T+H	6.9 (95% CI 5.3 to 9.9)																									
CRx	4.6 (95% CI 4.4 to 5.4)																									
AC	6.1(95% CI 4.9 to 7.1)																									
T	2.7 (95% CI 2.1 to 4.3)																									
CRx+H = 7.8	CRx = 4.6 (p<0.05)																									
AC+H = 8.1	AC = 6.0 (p<0.05)																									
T+H = 7.1	T = 3.0 (p<0.05)																									
CRx+H = 10.0	CRx = 5.6																									
AC+H = 9.3	AC = 5.9																									
T+H = 10.9	T = 4.6																									
<p>Outcome 4: Survival at 1 year</p> <p>CRx+H = 79.1% vs CRx = 68.4% (p<0.05) AC+H = 83.2% vs AC = 73.2% (p<0.05) T+H = 72.8% vs T 61.5%</p> <p>One year mortality rates (ITT):</p> <p>Commercial in confidence information removed from paragraph.</p> <p>CRx+H = 20.9% (95% CI 15.7 to 26.0) vs CRx = 31.6% (95% CI 25.7 to 37.6) p<0.0080</p> <p>Commercial in confidence information removed from paragraph.</p>	<p>Outcome 5: Overall survival</p> <p>For all participants (ITT)</p> <p>CRx+H = 25 vs CRx = 20 (p<0.05) AC+H = 27 vs AC = 21 T+H = 22 vs T = 18</p> <p>For participants with HER2 3+ (n=349)</p> <p>CRx+H = 29 (p<0.05) vs CRx = 20 AC+H = 31 (p<0.05) vs AC = 21 T+H = 25 vs T = 18</p> <p>Median survival time in months (ITT analysis)</p> <p>Survival was censored for patients who were alive at data cut-off (Oct 1999). This calculation included patients in the group given chemotherapy alone who received open-label trastuzumab after the</p>	<p>Outcome 6: Complete response</p> <p>Complete response was defined as disappearance of all radiographically and/or visually apparent tumour. Commercial in confidence information removed from paragraph.</p> <p>Follow up time: Data cut-off point 31 December 1997 (minimum follow-up of 9 months).</p> <p>CRx+H = 18/235 (8%) H+ AC = 11/143 (8%); H+T = 7/92 (8%) CRx = 8/234 (3%) AC = 6/138 (4%); T = 2/96 (2%)</p>																								

	<p>occurrence of disease progression.</p> <p>Commercial in confidence information removed from paragraph.</p>																																								
<p>Outcome 7: Partial response Partial response was defined as a decrease of more than 50 percent in the dimensions of a measurable lesion. Commercial in confidence information removed from paragraph.</p> <p>Follow up time: Data cut-off point 31 December 1997 (minimum follow-up of 9 months).</p> <p>CRx+H = 100/235 (43%) H+ AC = 69/143 (48%); H+T = 31/92 (34%) CRx = 66/234 (28%) AC = 52/138 (38%); T = 14/96 (15%)</p>	<p>Outcome 8: Overall tumour response (ITT analysis) Defined as complete or partial response. Commercial in confidence information removed from paragraph.</p> <p>Follow up time: Data cut-off point 31 December 1997 (minimum follow-up of 9 months).</p> <p>For all participants (ITT) CRx+H = 118/235 (50%, 95% CI 44 to 57) vs CRx = 74/234 (32%, 95% CI 26 to 38) p<0.001 H+ AC = 80/143 (56 %, 95% CI 48 to 64) vs AC = 58/138 (42%, 95% CI 34 to 50) p=0.02 H+T = 38/92 (41%, 95% CI 31 to 51) vs T = 16/96 (17%, 95% CI 9 to 24) p<0.001</p> <p>For participants with HER2 3+ (n=349) CRx+H = 56% CRx = 31% AC+H = 60% AC = 42% T+H = 49% T = 17</p>	<p>Outcome 9: Incidence of CREC-diagnosed cardiac dysfunction</p> <p>For the assessment of this adverse event the independent, blinded Cardiac Review and Evaluation Committee (CREC) was formed post hoc to review all cases of known or suspected cardiac dysfunction. The committee was composed of two oncologists and one cardiologist.⁶⁵</p> <p>Commercial in confidence information removed from paragraph.</p>																																							
<p>Results of HRQL reported by Baselga et al., 1999⁸⁶</p>																																									
<p>Outcome 10: HRQL .HRQL was assessed using the EORTC QLQ-C30 (version 1.0) with the breast cancer module (BR-23) at baseline, and at week 8, 20, and 32.⁸⁶ At baseline, 431 of 469 (92%) participants completed the questionnaire. At subsequent time points, the numbers of regularly scheduled questionnaires completed were 360 of 390 (95%) at week 8, 282 of 320 (88%) at week 20, and 160 of 181 (88%) at week 32.³⁰</p> <p>For HRQL five prospectively defined domains (physical, role, social, global quality of life and fatigue) were defined as primary. All remaining domains were secondary (pain, nausea/vomiting, cognitive, emotional, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties, body image, sexual functioning, sexual enjoyment, future perspective, arm symptoms, breast symptoms, systemic therapy side effects and upset by hair loss). Data were analysed via repeated measures ANOVA using the last observation carried forward (death was assigned a value of '0'). Missing data at week 8 or 10 were not included in the analysis.</p>	<p>Changes in Health-Related Quality-of-Life Scores at baseline and week 32³⁰</p> <table border="1"> <thead> <tr> <th></th> <th>Baseline Mean (± SE) n=207</th> <th>week 32 Mean (± SE) n = 207</th> </tr> </thead> <tbody> <tr> <td>CRx + H</td> <td></td> <td></td> </tr> <tr> <td>Global QOL</td> <td>59.3 ± 1.8</td> <td>1.2 ± 2.0</td> </tr> <tr> <td>Physical function</td> <td>71.5 ± 1.9</td> <td>-2.9 ± 2.1</td> </tr> <tr> <td>Social function</td> <td>68.0 ± 2.1</td> <td>0.9 ± 2.2</td> </tr> <tr> <td>Role function</td> <td>64.6 ± 2.5</td> <td>-3.2 ± 2.8</td> </tr> <tr> <td>Fatigue</td> <td>37.6 ± 1.9</td> <td>1.1 ± 2.2</td> </tr> <tr> <td>CRx</td> <td>n=194</td> <td>n = 194</td> </tr> <tr> <td>Global QOL</td> <td>58.4 ± 1.8</td> <td>-3.9 ± 2.0</td> </tr> <tr> <td>Physical function</td> <td>70.6 ± 2.1</td> <td>-8.0 ± 2.3</td> </tr> <tr> <td>Social function</td> <td>68.1 ± 2.2</td> <td>-4.5 ± 2.4</td> </tr> <tr> <td>Role function</td> <td>66.2 ± 2.7</td> <td>-9.3 ± 2.9</td> </tr> <tr> <td>Fatigue</td> <td>36.9 ± 2.0</td> <td>6.7 ± 2.1</td> </tr> </tbody> </table> <p>A negative number indicates worsening for global QL, physical, role and social functioning, and an improvement for fatigue.</p> <p>There was no significant difference between the groups for all five predetermined scales at the level of p=0.01.</p>		Baseline Mean (± SE) n=207	week 32 Mean (± SE) n = 207	CRx + H			Global QOL	59.3 ± 1.8	1.2 ± 2.0	Physical function	71.5 ± 1.9	-2.9 ± 2.1	Social function	68.0 ± 2.1	0.9 ± 2.2	Role function	64.6 ± 2.5	-3.2 ± 2.8	Fatigue	37.6 ± 1.9	1.1 ± 2.2	CRx	n=194	n = 194	Global QOL	58.4 ± 1.8	-3.9 ± 2.0	Physical function	70.6 ± 2.1	-8.0 ± 2.3	Social function	68.1 ± 2.2	-4.5 ± 2.4	Role function	66.2 ± 2.7	-9.3 ± 2.9	Fatigue	36.9 ± 2.0	6.7 ± 2.1	<p>By week 32, there were trends for improvement in all five primary as well as secondary domains. None of these differences in the primary domains reached statistical significance. However, significant differences were found in the pain domain and dyspnoea question of the QLQ C-30 and the systemic therapy side effects domain of the BR-23, all favouring the CRx+H. (Baselga et al., 1999)⁸⁶</p>
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APPENDIX 7: TRASTUZUMAB MONOTHERAPY STUDIES INCLUDED IN THE UPDATE

Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
<p>Baselga et al., 1996¹⁷ (data was also obtained from Baselga et al., 1999³² and cardiac data was obtained from a non systematic review of trastuzumab studies published by Baselga, 2000)³³ US</p> <p>Study H0551g</p> <p>Study design: Case series (Phase II)</p> <p>Setting: Not stated</p> <p>Objective: To determine the antitumour activity of trastuzumab in patients with HER-2 overexpressing metastatic breast cancer (MBC), as well as define further the toxicity and pharmacokinetics of trastuzumab.</p>	<p>Inclusion criteria: Women with extensive metastatic breast cancer (MBC). HER2 overexpression at level 2+ or 3+ confirmed by a immunohistochemical (IHC) analysis. All participants had to have measurable disease, a Karnofsky performance status of at least 60% and preserved haematologic, liver, renal, and pulmonary function.</p> <p>Exclusion criteria: Patients with lymphangitic pulmonary metastasis, history of brain metastasis, or bone metastases as the only site of measurable disease. Chemotherapy or additive hormonal therapy within 3 weeks before study entry (6 weeks for mitomycin or nitrosureas) was not permitted.</p> <p>Patient population: 46 women with a mean age of 50 years (range 30-65 years). 39 (84.8%) participants had tumours overexpressing HER2 at level 3+. 16 (34.5%) participants had ≥ 3 metastatic sites. Previous therapy included: adjuvant chemotherapy (n=26, 56.5%), neoadjuvant chemotherapy (n=4, 8.7%), chemotherapy for metastatic disease (n=38, 82.6%), adjuvant hormonal therapy (n=7, 15.2%) and hormonal therapy for metastatic disease (n=21, 45.6%).</p>	<p>Intervention: Trastuzumab at a loading dose of 250mg iv, then 10 weekly doses of 100mg. Participants with no disease progression at the completion of this treatment period were offered a maintenance phase of 100mg/week.</p> <p>Concurrent treatment: Not stated</p> <p>Duration of follow up: Not stated</p> <p>Outcome measures:</p> <ul style="list-style-type: none"> <input checked="" type="checkbox"/> Response <input checked="" type="checkbox"/> Progression free survival <input checked="" type="checkbox"/> Overall survival <input checked="" type="checkbox"/> Quality of life <input checked="" type="checkbox"/> Adverse effects 	<p>Data on trastuzumab pharmacokinetics was available for 45 participants and the number of participants assessable for treatment response was 43. The reason participants were not assessable for response included bacterial infection of an intravenous catheter that required prolonged administration of antibiotics (which precluded treatment with trastuzumab), refusal to continue on study due to personal reasons, and death due to congestive heart failure associated with prior doxorubicin treatment.</p>	<p>All responses were confirmed by an independent extramural evaluation committee composed of an oncologist and radiologist.</p> <p>Confidence intervals for response rates were calculated using the exact method for a single proportion.</p> <p>Complete response was defined as the disappearance of radiographically, palpable, and/or visually apparent tumour. Partial response was defined as a ≥ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Disease progression was defined as a ≥ 25% increase in any measurable lesion or the appearance of a new lesion. Although bone metastases were not considered measurable for response, participants were required to have at least stable bone lesions to be considered responders.</p> <p>Overall responses were seen in five participants, which included one complete remission and four partial remissions (overall response rate was 11.6%, 95% CI: 4.36 to 25.9%). Responses were observed in liver, mediastinum, lymph nodes, and chest wall lesions. Minor responses, seen in two participants, and stable disease, which occurred in 14 participants, lasted for a median of 5.1 months. 22 participants had progression of disease.</p> <p>Adequate pharmacokinetic levels of trastuzumab were obtained in 90% of the participants. Toxicity was minimal and no antibodies against the monoclonal antibody (rhuMAb HER2) were detected in any participant. One participant experienced grade 3 (based on a modified National Cancer Institute common toxicity criteria) pain at tumour site.</p>	<p>Author's conclusions: Trastuzumab is well tolerated and clinically active in patients with HER2-overexpressing MBCs that had received extensive prior therapy. This is evidence that targeting growth factor receptors can cause regression of human cancer and justifies further evaluation of this agent.</p> <p>Other comments: The length of follow-up is not reported.</p>

				Three participants had cardiac dysfunction, two of whom died. ³³	
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Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
<p>Cobleigh et al., 1999²⁵ (data was also obtained from the Roche report⁸ and an abstract published by Cobleigh, 1999³⁵ Information (quality of life data) on the study was also presented in Osoba & Burchmore, 1999³⁰ and Lieberman et al., 1999.³⁶ Interim results were presented in as an abstract by Cobleigh et al., 1998.³⁷ US</p> <p>Study H0649g</p> <p>Study design: Case series (Phase II)</p> <p>Setting: Out patients setting. Multicentre study with 54 centres in US, Canada, Belgium, France, Germany, UK and Australia,</p> <p>Objective: To determine the overall objective response rate to trastuzumab treatment as a single agent and to further characterise the safety profile of trastuzumab.</p>	<p>Inclusion criteria: Women with advanced metastatic breast cancer (MBC). HER2 overexpression at level 2+ or 3+ confirmed by a immunohistochemical (IHC) analysis.</p> <p>Exclusion criteria: Presence of untreated brain metastasis, bone metastases as the only disease site, concomitant malignancy not curatively treated, a Karnofsky performance status less than 60%, participants who were pregnant, nursing, or if they had used investigational or unlicensed agents within 30 days.</p> <p>Patient population: 222 women with a mean age of 50 years (range 28-81). 50 had HER2+ overexpression and 172 had HER3+. 76 (36%) participants had ≥3 metastatic sites and 155 (72%) had metastatic involvement of the liver and lung. 86 (40%) participants had a disease free interval (DFI) >24 months and 80 (37%) had DFI less than 12 months. Out of 214 participants, 146 (68%) had received prior adjuvant chemotherapy and 214 prior chemotherapy for MBC (69 of whom had only received one regimen and 145 two or more regimens). Most had received both prior anthracycline (n=201, 94%) and taxane (n=143, 67%) therapy, and 26% had undergone high-dose chemotherapy with bone marrow or stem-cell rescue. 151 (71%)</p>	<p>Intervention: Trastuzumab used for second or third line therapy. The loading dose was 4mg/kg iv, followed by a 2mg/kg maintenance dose at weekly intervals. If participants developed disease progression, the investigator could continue with 2mg/kg, increase the dose to 4mg/kg, or discontinue treatment. The median number of infusions was 12 (range, 1 to 96).</p> <p>Concurrent treatment: Additional antitumour therapy was permitted at disease progression. Acetaminophen and/or diphenhydramine was used for infusion related adverse events.</p> <p>Duration of follow up: Median follow-up was 12.8 months (final analysis 15 months after enrolment of the last patient)</p> <p>Outcome measures: <i>Primary outcome measure:</i> <input checked="" type="checkbox"/> Response <i>Secondary outcome measures:</i> <input checked="" type="checkbox"/> Progression free survival <input checked="" type="checkbox"/> Overall survival <input checked="" type="checkbox"/> Quality of life (QoL) <input checked="" type="checkbox"/> Adverse effects</p>	<p>222 participants were enrolled, of which 213 received at least one dose of trastuzumab. Nine participants were not treated for the following reasons: brain metastases (n=3), laboratory abnormality (n=2), adverse events (n=1), refusal to participate (n=1), clinical instability (n=1), and death (n=1). As of the cut-off date, 179 participants (81%) had discontinued the study, 14 participants (6%) remained in the study without disease progression, and 29 participants (13%) were continuing treatment after disease progression.</p> <p>Chemotherapy was added to trastuzumab in 36 patients after disease progression.</p> <p>Six participants (3%) discontinued the study because of adverse events, four before disease progression and two after disease progression. One participant developed an anaphylactoid reaction during the first dose. One participant withdrew from treatment after developing tuberculosis, and one participant withdrew from treatment because of atherosclerotic heart disease.</p>	<p>Time to event end points were estimated by Kaplan-Meier survival methodology. The effect of baseline characteristics on response rates was evaluated by the chi-squared test and logistic regression model. The risk factors for time to progression were determined by the Cox proportional hazards regression model.</p> <p>Overall response was determined by a blinded independent response evaluation committee (REC). Any potential cardiac events were evaluated retrospectively, by a blinded independent Cardiac Review and Evaluation Committee (CREC).</p> <p>Complete response was defined as the disappearance of radiographically, palpable, and/or visually apparent tumour. Partial response was defined as a ≥ 50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions. Disease progression was defined as a ≥ 25% increase in any measurable lesion or the appearance of a new lesion. Time to treatment failure was defined as the time from enrolment to disease progression, death, treatment discontinuation, or initiation of a new antitumour therapy.</p> <p>According to the CREC, there were eight complete and 26 partial responses. The overall response rate for the intention to treat population (n=222) was 15% (95% CI, 11% to 21%). Participants whose tumours overexpress HER2 at the 3+ level tended to have higher response rates than those with a 2+ level of overexpression (18% vs 6%; p=0.06).</p> <p>According to the investigators, there were 12 minor responses (6%), 62 participants (29%) with stable disease, and 93 (44%) with progressive disease.</p> <p>The median duration of overall response (n=34) was 9.1 months (range 1.6 to >26 months)</p>	<p>Author's conclusions: Trastuzumab, administered as a single agent, produces durable objective responses and is well tolerated by women with HER2-overexpressing metastatic breast cancer that has progressed after chemotherapy for metastatic disease. Side effects that are commonly observed with chemotherapy, such as alopecia, mucositis, and neutropenia, are rarely seen.</p> <p>Other comments: This was a non-comparative study. Therapeutic effect can not be determined from this type of study.</p> <p>Despite the fact that the study was multicentre involving 54 different international centres only 222 participants were enrolled.</p> <p>The investigators were not blinded to the fact that the participants had received the intervention. Their measure of response and other outcome measures may therefore be biased or represent an overestimation (37 (17%) women had partial response according to the investigators compared to 26 (11%) according to the REC). A blinded committee (REC) was only used to measure the primary end point. However, a blinded independent cardiac review and evaluation committee (CREC) was established retrospectively to assess cardiac dysfunction.</p>

	<p>had received prior radiotherapy and 122 (57%) prior hormonal therapy.</p>			<p>months).</p> <p>The median time to disease progression (n=213) was 3.1 months (range, 0 to >28 months); the median time to treatment failure was 2.4 months (range 0, to >28 months). The median duration of survival (n=222) was 13 months.</p> <p>The most common adverse events, which occurred in approximately 40% of patients, were infusion-associated fever and/or chills that usually occurred only during the first infusion. The most clinically significant adverse event was cardiac dysfunction, which occurred in ten patients (4.7%). Only 1% of patients discontinued the study because of treatment-related adverse events.</p> <p>Adverse events that occurred in >10% of 213 participants treated with at least one dose of trastuzumab (including those not related to treatment) were as follows: Abdominal pain (n=4), asthenia (n=6), back pain (n=1), chest pain (n=3), chills (n=5), fever (n=2), headache (n=4), infection (n=1), pain (n=17), flu syndrome (n=1), pruritis (n=1), constipation (n=1), diarrhoea (n=3), nausea (n=2), vomiting (n=1), increased coughing (n=1), dyspnea (n=10).</p> <p>Laboratory abnormalities Nine (4%) of 211 participants experienced grade 3 haematologic abnormalities, which were manifested by leukopenia (n=3), neutropenia (n=2), thrombocytopenia (n=3), or decreased hemoglobin (n=1). Twenty (9%) of 212 participants experienced at least one grade 3 hepatic laboratory abnormality and seven (3%) experienced at least one grade 4 hepatic laboratory abnormality.</p>	<p>The median follow-up was 12.3 months, which may be too short to make firm conclusions regarding the durability of response.</p> <p>It was reported that response rates were significantly higher among those whose time to 1st relapse was more than 6 months (20% vs 9%, p=0.03). However, the number of participants within each sub-series was not reported.</p>
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Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
<p>Vogel et al., 2001²⁶ (Accrual dates and median duration of response were obtained from Shak, 1999³⁴</p> <p>Study H0650g</p> <p>Study design: Single –blind RCT</p> <p>Setting: Multicentre study involving 19 North American centres.</p> <p>Objective: The primary objectives of the trial were to assess the overall response rate and safety associated with trastuzumab in patients with HER2-positive MBC</p>	<p>Inclusion criteria: Women with progressive metastatic breast cancer (MBC). HER2 overexpression at level 2+ or 3+ confirmed by a immunohistochemical (IHC) analysis. All participants had to have measurable disease and a Karnofsky performance Status (KPS) ≥ 70%.</p> <p>Exclusion criteria: Individuals with bone-only disease were excluded.</p> <p>Patient population: 113 women with a mean age of 54 years (range 28-86 years). 85 (76%) participant had tumours overexpressing HER2 at the 3+ level. 34 (30%) participants had ≥ 3 metastatic sites and 74 (66%) had metastatic involvement of the liver or lung. Median disease free interval (DFI) was 17 months with 30 (27%) participants having a DFI of <12 months. Previous therapy included: adjuvant chemotherapy (n=76, 68%), anthracycline use (n=62, 55%), radiotherapy (n=54, 48%), hormonal therapy (n=41, 37%) and high-dose chemotherapy plus stem-cell transplantation (n=13, 12%).</p> <p>The two groups were reported to be generally comparable in terms of baseline characteristics, but this information was not presented.</p>	<p>Intervention: Trastuzumab (used for first line therapy) at a standard lower dose (LD) regimen of 4mg/kg iv loading and 2mg/kg iv weekly until disease progression (n=58).</p> <p>Comparator: Trastuzumab (used for first line therapy) at a higher dose (HD) regimen of 8mg/kg iv loading and 4mg/kg iv weekly until disease progression (n=54).</p> <p>Concurrent treatment: None reported.</p> <p>Duration of follow up: Median follow-up was 11 months (range 1.2 to 35 months)</p> <p>Outcome measures: <i>Primary outcome measure:</i> <input checked="" type="checkbox"/> Response <input checked="" type="checkbox"/> Adverse effects <i>Secondary outcome measures:</i> <input checked="" type="checkbox"/> Progression free survival <input checked="" type="checkbox"/> Overall survival <input checked="" type="checkbox"/> Quality of life (QoL)</p>	<p>Data were available for 112 evaluable participants.</p>	<p>The investigators evaluated tumour response and safety. Any potential cardiac events were evaluated by an independent Cardiac Review and Evaluation Committee (CREC).</p> <p>In the LD group there were two complete (CR) and 12 partial responses (PR) compared to four CR and eight PR in the HD group. The overall response rates were: 14 (24%, 95% CI: 13 to 35%) in the LD group and 12 (22%, 95% CI: 11 to 33%) in the HD group.</p> <p>The number of participants with stable disease (SD) at > 6months were four in the LD group and five in the HD group.</p> <p>The overall response rate for participants with HER2 at level 3+ (n=85) was 26 (31%).</p> <p>The Kaplan-Meier estimate of the median duration of the response was 9 months.³⁴</p> <p>Overall, the median time to progression (TTP) was 3.4 months and 8 months in those achieving CR and PR. For participants with SD at > 6 months TTP was 10.8 months. At a median follow-up of 11 months, 67% of participants were alive with survival duration ranging from 1.2 to 35.3 months.</p> <p>Adverse events were mainly mild to moderate in nature. Severe adverse events included: asthenia (LDG: 2; HDG: 4), chills (LDG: 0; HDG: 1), fever (LDG: 1; HDG: 0), headache (LDG: 1; HDG: 1), diarrhoea (LDG: 1; HDG: 3), and vomiting (LDG: 1; HDG: 2).</p> <p>One participant had cardiac dysfunction (cardiac symptoms or asymptotic decrease (>10%) in ejection fraction) according to the independent cardiac review and evaluation committee (CREC).</p>	<p>Author's conclusions: Trastuzumab has been shown to be active as a single agent in HER2-positive patients who had received no previous chemotherapy for metastatic breast cancer. Trastuzumab is well tolerated and common chemotherapy-associated adverse events, such as myelosuppression and mucositis, were rare.</p> <p>Other comments: This study was also reported as an abstract (Vogel et al., 2000).³⁸ However, the results in the two publications differed and therefore the information in the abstract was not used. 114 women were randomised according to Vogel et al., 2000.³⁸</p> <p>No information is presented on how participants were randomised and the baseline characteristics were not presented according to the randomised treatment groups.</p> <p>The investigators were not reported to have been blinded to the fact that the participants had received the intervention. Their measure of response and safety measures may therefore be biased or represent an overestimation as demonstrated in Study H0649g reported by Cobleigh et al., 1999²⁵</p> <p>All participants who had a complete or partial response demonstrated 3+ HER2 overexpression.</p>

APPENDIX 8: ONGOING TRASTUZUMAB TRIALS

Table: Ongoing and Planned Clinical Trials with Trastuzumab

Commercial in confidence information removed from table.

APPENDIX 9: ECONOMIC EVALUATION FOR TRASTUZUMAB

Study details	Source of data	Method for estimation of benefits/costs	Results/statistical analysis	Sensitivity analysis	Comments
<p>Roche, 2000⁸</p> <p>Research question: To evaluate the cost effectiveness of trastuzumab (T) in the licensed indication, which includes: 1) the comparison of trastuzumab, as a monotherapy with vinorelbine (V) for second line therapy of MBC. 2) the comparison of trastuzumab (T) plus paclitaxel (combination therapy) with paclitaxel (P) as a single agent for first line therapy of MBC.</p> <p>Type of economic evaluation: Monotherapy: Cost effectiveness analysis</p> <p>Combination therapy: Cost effectiveness analysis, cost utility analysis</p> <p>Country/currency UK /£ sterling</p> <p>Cost year: 2000</p> <p>Perspective: NHS</p> <p>Study population: Mono: 222 patients with heavily pre-treated HER2 positive metastatic breast cancer (H0649g). Combination therapy: 469 patients receiving first-line treatment for HER2 positive metastatic breast cancer</p>	<p>Source of effectiveness data: Monotherapy: a non-randomised controlled trial H0649g⁸ (+ H0650g).⁸</p> <p>Combination therapy: a RCT of trastuzumab plus chemotherapy versus chemotherapy alone, study H0648g⁸ (see effectiveness section). Vinorelbine from a single RCT comparing vinorelbine to Melphalan as second line therapy for MBC (Jones et al., 1995).⁷¹</p> <p>Source of cost data: Mono: Resource use and cost data come from clinical trial H0649g for Trastuzumab,²⁸ and from Jones et al., 1995⁷¹ for Vinorelbine. Outpatient costs were based on Unit costs of Health and Social Care PSSRU 1999, inflated to 2000 figures.</p> <p>Combination therapy: Resource use and unit costs for the combination therapy were estimated using national databases, published literature and hospital specific data.</p>	<p>Valuation for clinical outcomes or benefits: Mono: Primary: Overall response rate (complete and partial) as determined by an independent and blinded response evaluation committee (REC) and the safety profile. Secondary: duration of response, 1-yr survival, time to disease progression, time to treatment failure and quality of life (using the EORTC QLQ-C30).</p> <p>Combination therapy: Primary: time to disease progression. Secondary: response rate, duration of response, 1-yr survival and quality of life. UK-specific utility estimates associated with the disease states were taken from a published study (Hutton et al., 1996), using the standard gamble technique. Measures of benefit: Life years gained (LYG) and Quality adjusted life years gained (QALY). Commercial in confidence information removed from paragraph.</p> <p>Estimation of costs: The costs used include the following: Mono: drug costs, outpatient costs (Unit costs of Health and Social Care PSSRU 1999), adverse events costs. The number of outpatient visits was assumed to be equal to the number of doses received (12 for T and 8 for V).</p>	<p>Clinical outcome/ benefits: Monotherapy: response rate (+3 HER overexpressors) is 18% (95% CI 12.6, 24.6) for Trastuzumab. Overall survival was 16.4 months (range 12.3, no end point). For vinorelbine a response rate of 16% was reported, and median survival was 8.1 months. Commercial in confidence information removed from paragraph.</p> <p>Combination therapy: RCT data a response rate (+3 HER overexpressors) of 56% for Trastuzumab and chemotherapy (H+CRx) compared to 31% for CRx alone. The median duration of response was 10.0 months for H+CRx compared to 5.6 for CRx and the median time to progression 7.8 months for H+CRx compared to 4.6 for CRx; overall survival was 29 months for H+CRx compared to 20 for CRx.</p> <p>Commercial in confidence information removed from paragraph.</p> <p>Costs: Monotherapy: Drug costs: Overall drug costs for T was £5296 versus £1191 for V. NHS outpatient costs for H was £900 versus £600 for V. Costs for the management of adverse events for H were £0 versus £22 for V. Total cost per patient for T are £6196 versus £1812 for Vinorelbine.</p> <p>Combination therapy: Total costs for T+P are £28,600 and for P are £10,900.</p>	<p>Sensitivity analysis: Monotherapy: mitomycin (M) was used as alternative comparator: Cost per LYG for T=£8505.</p> <p>Combination therapy: All major assumptions were subjected to sensitivity analysis (key parameters: time horizon, costs, utilities and efficacy rates). The two time horizons chosen were 5 and 0 years. Base case cost per QALY are most sensitive to utility weights assumptions; the cost effectiveness ratios are quite sensitive to the time horizon of the survival extrapolation.</p> <p>Appropriateness: Sensitivity analysis of T vs. V could have been expanded. Sensitivity analyses of T+P vs. P was reported in detail</p>	<p>Author's conclusions: Monotherapy: CEA for T vs vinorelbine showed an incremental cost per LYG of £7,521 in favour of T. Combination therapy: CEA for T+P vs paclitaxel showed an incremental cost per LYG for T of £14,069 with an associated cost per QALY of £29,448.</p> <p>Trastuzumab used earlier in the course of the disease in combination with paclitaxel brings considerable benefit with an increase in overall survival, at the cost of very little additional toxicity and no deficit in quality of life.</p> <p>Magnitude and direction of result: A: for both monotherapy and combination therapy.</p> <p>Comments: Monotherapy: Effectiveness data was not based on a RCT of T. A head to head comparison of effectiveness data was not used as the information relating to T was from a different study to that of V. The V trial was a RCT. It was not stated why LYG and not QALY were used for monotherapy. This means that the effectiveness data is based solely on median survival data. Bearing in mind the poor prognosis of heavily pre treated individuals with MBC, the use of QALY may be a better measure of benefit. Only life threatening toxicities were taken into account when evaluating the cost of adverse effects (cardiotoxicity and</p>

<p>(H0648g).</p> <p>Interventions (including comparator): Trastuzumab (+paclitaxel) Vinorelbine, paclitaxel</p>		<p>Combination therapy: UK costs for the time spent in each health state within the model were based on published estimates (Brown and Burrell, 1999). Standard costs were applied from national databases, published literature and hospital specific data. Additional costs include drug costs (taken from MIMS, October 2000).</p> <p>How the actual costs were estimated was not stated for either mono or combination therapy</p> <p>Commercial in confidence information removed.</p> <p>Modelling: Monotherapy: It was stated that costs were modeled and only direct medical costs tot he NHS were included. The time horizon used was 2 years.</p> <p>Combination therapy: The analysis is based on a health state transition model which calculates time in different health states from Kaplan-Meier estimates. Utilities and direct medical costs associated with these health states are used, together with clinical efficacy data. Commercial in confidence information removed from paragraph.</p>	<p>Synthesis of costs and benefits: Incremental cost per life year gained (LYG) of T vs. V: £7,521; T+P vs. P is £14,069. Incremental cost per quality of life year gained (QALY) for T+P vs P is £29,448.</p> <p>Statistical analysis: NA</p>	<p>neutropenia). The cost for adverse effects for T was taken as £0 (due to reported cardiotoxicity being low) and this was not explored in a sensitivity analysis. T was found to be associated with cardiac dysfunction in the effectiveness study, the cost of which was not considered. Further uncertainties around the data could have been explored in a more extensive sensitivity analysis. The authors did not vary the circumstances (e.g. price and effectiveness outcome measures) of the included drugs, they only used an alternative comparator (M) that had the same median survival estimate as vinorelbine.</p> <p>Combination therapy: The RCT that the effectiveness data is based on included 469 participants. Only 188 of these participants were included in the comparison of H+P vs P and of these only those who had HER2 overexpressing MBC at level 3+ were included. At disease progression all participants were allowed to receive T as part of the follow-on protocol H0659g. 75% of participants who received P alone switched to T+P after disease progression. Commercial in confidence information removed from paragraph.</p> <p>The vinorelbine trial conducted by Jones et al., 1995.⁷¹ and the trastuzumab trial H0649g²⁸ are included in the effectiveness section of the review.</p>
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APPENDIX 10: INDUSTRY SUBMISSION DATA PRESENTED TO NICE

Industry Submission Data from Roche.

Effectiveness data

The submission data was based on two studies. One study (Roche study H0649g) was a non-randomised study of monotherapy in participants with heavily pre-treated HER2 positive MBC (n=222). This study was not initially included in the review, as it did not meet the inclusion criteria. However, when the review was updated, at the request of NICE this study was found to meet the new inclusion criteria for monotherapy. The second study was Roche study H0648g which was a RCT comparing the efficacy of chemotherapy alone versus in combination with trastuzumab in participants receiving first line therapy for MBC overexpressing HER2 (n=469). This trial²⁸ was already included in the review and additional data was extracted from the industry submission report (see Appendix 6 data extraction tables for trastuzumab). At disease progression participants were allowed to enroll in the follow-up protocol (Roche study H0659g) which permitted all participants to receive trastuzumab. The results of the follow-up study were not included in the current NICE review, as it does not meet the inclusion criteria. The submission data included a reference to a published abstract of a RCT of trastuzumab used at different doses conducted by Vogel et al.³⁸. This trial was excluded from the initial review as it did not have a control group receiving systemic therapy without trastuzumab. However, it did meet the inclusion criteria for the update review and has now been included under trastuzumab monotherapy.

Economic data

The industry submission included a cost effectiveness analysis that compared the use of trastuzumab as a single agent with vinorelbine, and a cost utility and cost-effectiveness analysis of trastuzumab as part of a combination therapy (trastuzumab plus paclitaxel) compared with the single agent paclitaxel. These are included in the review of economic data.