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The clinical effectiveness of trastuzumab for breast cancer: a systematic review

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The clinical effectiveness of trastuzumab for breast cancer: a systematic review

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

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, for example, 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.

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.

Case series In this report, the term case series has been used to denote Phase II studies that are uncontrolled prospective studies.

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.

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

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 that 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.

continued

Glossary *contd*

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.

Grading of breast cancer Grading refers to the appearance of the cancer cells under the microscope. The grade gives an idea of how quickly the cancer may develop. There are three grades: grade 1 (low grade), grade 2 (moderate grade) and grade 3 (high grade).

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 that has infiltrated the skin or chest wall or disease that 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 Tumour regression of ≥ 25%–< 50% for all measurable tumours for ≥ 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-ray or computed tomography 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.

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, for example, pleural effusions or ascites.

Overall response A complete or partial response.

Oestrogen receptor 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 that are not.

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

Partial response A decrease in tumour size of ≥ 50% 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).

Performance status A measure of how the disease affects the daily living abilities of the patient.

continued

Glossary *contd*

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 defining appropriate action.

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.

Randomised controlled trial An experimental study in which subjects are randomised to receive either an experimental or a control treatment or intervention. The relative effectiveness of the intervention is assessed by comparing event rates and outcome measures in the two groups.

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, that is, 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 < 25% change in measurable lesions for ≥ 4–8 weeks with no new lesions appearing.

Staging The allocation of categories (stages 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.

United Kingdom Coordinating Committee on Cancer Research The national committee responsible for coordinating clinical trials for cancer treatment in the UK.

List of abbreviations

ABC	advanced breast cancer
CCTR	Cochrane Controlled Trials Register
CI	confidence interval
CMF	cyclophosphamide plus methotrexate plus 5-fluorouracil
CREC	Cardiac Review and Evaluation Committee
HDG	high-dose group
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HRQoL	health-related quality of life
IHC	immunohistochemistry
ISTP	Index to Scientific and Technical Proceedings
ITT	intention-to-treat
i.v.	intravenous/intravenously*
LDG	low-dose group
MBC	metastatic breast cancer
NA	not applicable
NICE	National Institute for Clinical Excellence
OR	overall response
QoL	quality of life
RCT	randomised controlled trial
REC	Response Evaluation Committee
RR	relative risk
SE	standard error*

* Used only in tables and appendices

Executive summary

Background

Breast cancer is the leading cause of cancer deaths amongst women in the UK. Figures suggest that about 13% of women initially presenting with breast cancer have advanced disease (stage III/IV) and about 50% presenting with early or localised breast cancer will eventually progress to advanced disease.

The prognosis of metastatic breast cancer (MBC) depends on age, extent of disease, oestrogen receptor status and previous chemotherapy treatment. There is also evidence that the over-expression of the product of the 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 quality of life (QoL) with as little treatment-related toxicity as possible. Trastuzumab (Herceptin®, Genentech Inc, South San Francisco, CA, USA), a recombinant humanised monoclonal antibody that specifically targets the epidermal growth factor receptor 2 (HER2) protein, 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.

Objective

The objective of the review was to evaluate the effectiveness of trastuzumab in the management of breast cancer.

Methods

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

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, and these data have subsequently been added.

Several databases were searched using strategies designed specifically for each database. Additional references were identified through reviewing manufacturer and sponsor submissions made to NICE, the bibliographies of retrieved articles, conference proceedings and by searching the Internet.

Data were extracted by one reviewer and checked by a second. 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 tumour response, QoL, time to disease progression, overall survival and relief of symptoms. Studies were grouped according to the type of intervention (monotherapy or combination therapy).

Results

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 HER2-overexpressing 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, longer progression-free survival and greater complete and overall tumour response when compared to chemotherapy alone. There was a significantly greater incidence of congestive heart failure reported among

those receiving trastuzumab plus chemotherapy compared to those on chemotherapy alone. The incidence seemed to be highest with trastuzumab plus anthracycline (approximately one-quarter of participants), rather than with trastuzumab plus paclitaxel. (Information relating to the results of a subgroup analysis was marked as confidential and was, therefore, removed from the review.)

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 tumour response (partial and complete), which ranged from 12 to 24% in the three studies. An independent response committee assessed tumour response outcomes in two studies, whereas tumour response was assessed by the investigators in the third study (H0650g). Similar durations of tumour response were reported by two studies of 9 (study H0650g) and 9.1 months (study H0649g).

Only one study (H0649g) reported the number of complete (five (3%)) or partial (26 (15%)) tumour responses for participants with tumours overexpressing HER2 at level 3+. In study H0650g, the overall tumour response rate for this group of participants was reported for both treatment groups combined as 31% (26/85). These results demonstrated that the majority of tumour responses occurred in participants with tumours over-expressing HER2 at level 3+.

Two studies reported data on survival endpoints (H0649g and H0650g). Study H0649g reported the overall median survival time using Kaplan–Meier methodology as 13 months (range 0.5–30), and that for participants with tumours overexpressing HER2 at level 3+ as 16.4 months. The median follow-up for this study was 12.8 months. In 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 appeared to have a relatively low toxicity level.

Conclusions

Trastuzumab when used in combination with chemotherapy seemed to be more effective than chemotherapy alone for the treatment of MBC overexpressing HER2 at level 3+ in individuals who had not received prior treatment for MBC. However, it seemed to be associated with congestive heart failure, particularly in patients that received anthracycline-based chemotherapy.

Trastuzumab monotherapy when used as second-line or subsequent therapy for the treatment of MBC overexpressing HER2 at level 3+ appeared to have some antitumour effects in terms of overall tumour response based on non-comparative studies (which provide relatively weak evidence) of moderate quality.

Implications for further research

Further large well-conducted RCTs are required to provide more evidence of the effectiveness of trastuzumab when used within its licensed indications, in addition to other indications.

Chapter 1

Objective and background

Objective of the review

The objective of the review was to evaluate the clinical effectiveness of trastuzumab (Herceptin®, Genentech Inc, South San Francisco, California, USA) in the management of advanced breast cancer.

Description of the underlying health problem

Breast cancer is the leading cause of death amongst women aged 35 to 54 years in the UK.[2] It is the most common cause of death due to malignancy, with over 13,000 deaths reported in 1998.[3] About 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 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 about 13% of women initially presenting with breast cancer have advanced disease[6] (stage III or IV, see appendix 1) and approximately 50% of patients presenting with early or localised breast cancer will eventually progress to develop advanced disease (stage III or IV).[7,8]

The risk of metastatic breast cancer (MBC), that is, stage IV, relates to known prognostic factors in the original primary tumour. These factors include grade of tumour, oestrogen receptor-negative disease, primary tumours ≥ 3 cm 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] grade of tumour 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) that 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 tests (HER2 2+) should have this confirmed with a test based on gene amplification techniques, known as the fluorescent in-situ hybridisation test.[13]

MBC is considered to be incurable. Median survival after diagnosis of advanced breast cancer (ABC), that is, stage III or IV, has been reported to be 18–24 months.[14] 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.[15] Treatment is, therefore, usually focused on relieving symptoms and improving the quality of life (QoL) with as little treatment-related toxicity as possible.

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 5-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. < 1 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 subgroup 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.

Description of the technology

Identification of patients and criteria for treatment

Trastuzumab is used in patients with MBC who have tumours that overexpress HER2. Although about 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 that form the well-defined 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.[16] Scores of 2+ and 3+ indicate weak and strong overexpression or HER2, respectively. A score of 2+ is considered to indicate that > 10% of tumour cells have weak–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.[17] Alternatively, 25–50% 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+.[18]

Intervention

Trastuzumab (Herceptin) 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.[19]

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) in the following treatment modes.

- 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 150 mg vial. This equates to an average cost for a typical patient receiving monotherapy treatment of £5296 and for a patient receiving combination therapy of £15,481.[8]

Summary of current manufacturers information provided for health professionals[20]

Recommended dosage

An initial loading dose of 4 mg/kg body weight and subsequent weekly doses of 2 mg/kg body weight (beginning 1 week after the loading dose) are administered as 90-minute intravenous infusions. If the initial loading dose is well tolerated, subsequent doses may be administered over 30 minutes (see *Special warnings and special precautions for use* section). 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.

Contraindications

- 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.
- 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.[21]

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.

Chapter 2
Methods

Objective

The objective of the review was to evaluate the clinical effectiveness of trastuzumab (Herceptin) in the management of ABC. Only randomised controlled trials (RCTs) of trastuzumab alone or in combination with other agents versus systemic therapy without trastuzumab were initially considered in the assessment of clinical effectiveness.

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. These data have subsequently been added to this review. Only participants who had either been pretreated with an anthracycline and/or a taxane or for whom these treatments were unsuitable were included in this update.

Inclusion and exclusion criteria

Titles and, where possible, abstracts of studies identified from all searches and sources (see appendix 2) 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 criteria listed below. Studies that did not meet all of the criteria were excluded and their bibliographic details were listed along with the reason for exclusion. Information relating to inclusion of trials highlighted by the industry submissions is presented in appendix 3. Any disagreements were discussed in order to obtain a consensus and if no agreement was reached a third reviewer was consulted.

Interventions

Trastuzumab (Herceptin) alone or in combination with other agents versus systemic therapy without trastuzumab were included in the review. 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 versus 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 Union Internationale Contre le Cancer (International Union Against Cancer) staging system (see appendix 1).

When updating the review, only participants who had breast cancer overexpressing HER2 at level 3+ that had been previously treated with an anthracycline and/or a taxane or those for whom these treatments were unsuitable were included in the review.

Studies

The ultimate standard for the evaluation of medical treatments is the randomised controlled Phase III clinical trial.[22] For the evaluation of clinical effectiveness, only 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.[23]

Outcome measures

The following outcome measures were included in the review:

- tumour response (including complete response and partial response)
- progression-free survival
- overall survival
- symptom relief
- QoL
- 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).

Search strategy

The databases searched for relevant literature were MEDLINE, EMBASE, CANCERLIT, BIOSIS, Index to Scientific and Technical Proceedings (ISTP), Cochrane Controlled Trials Register (CCTR), DARE, NHS EED and National Research Register. More detailed information about the search strategies are presented in appendix 2.

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.

Data extraction strategy

Data extraction was conducted by one reviewer using predefined data extraction forms in a Microsoft Access database (Microsoft Corporation, USA) 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, German, Dutch and French were included in the report. However, the search strategy included all languages and the bibliographic details of non-English language studies were presented in a table of excluded studies.

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 (ITT) basis. For dichotomous outcome measures the relative risk (RR) was calculated. For time to event outcomes (e.g. survival), hazard ratios (HRs) were reported if given in the paper as well as median values and any measures of variance presented.

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 (first- or second-/third-line), dosage regimen used and study design. Due to heterogeneity (based on the judgement of the differences mentioned above) being present, pooling of the results was deemed inappropriate. No formal statistical analysis of heterogeneity was undertaken due to the limited number of included studies.

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.

Confidentiality

Some information that was submitted to NICE by Roche, the manufacturer of trastuzumab, was marked commercial in confidence. This information was initially included in the report, which was made available to the NICE appraisal committee. However, this information has now been removed from this document making it available for wider publication. It has been noted within the text where this information has been removed.

Chapter 3
Results

Quantity and quality of research available

The evidence base for trastuzumab is summarised in *Table 1*.[17,18,24,25]

Included studies

A summary of the included studies is presented in *Table 2*[26–37] (with further details presented in appendices 4 and 5).

Combination therapy

Only one RCT (Roche study H0648g) that investigated the use of trastuzumab as combination therapy was found that met the inclusion criteria.[17] Study participants were randomised to receive chemotherapy alone or in combination with trastuzumab. The type of chemotherapy that 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 MBC overexpressing HER2 at level 2+ or 3+ as determined by IHC, who had not received prior treatment for MBC.[17] The number of participants included in the trial was 469.

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

The primary endpoint was time to disease progression and secondary endpoints included tumour response rate, duration of tumour response, time to treatment failure, survival and QoL. The final analysis of the primary endpoint, time to disease progression, was performed 9 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 35 months (range 30 to 51).

For ethical reasons, participants were allowed to enrol into the follow-on protocol H0659g at the time of disease progression that permitted all patients to receive trastuzumab. Of the HER2 3+ level subgroup who were initially randomised to receive paclitaxel alone, 75% 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

TABLE 1 *The evidence base for trastuzumab*

Type of therapy	Number of trials
Trastuzumab as first-line treatment	One RCT of combined therapy[17]
Trastuzumab as first-, second- or third-line treatment	Two case series[18,24] and one RCT[25] (both intervention groups received trastuzumab at different doses) of monotherapy

TABLE 2 *Trastuzumab – summary of included studies*

Source of trial data	Accrual dates	Number 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.*[17] and meeting abstracts[26–30])	June 1995–March 1997	469	First line	Trastuzumab plus chemotherapy (either cyclophosphamide plus anthracycline or paclitaxel)	Chemotherapy alone (either cyclophosphamide plus anthracycline or paclitaxel)
Trastuzumab as monotherapy					
Study H0551g (two published papers by Baselga *et al.*[18,31] and a non-systematic review of trastuzumab studies published by Baselga, 2000.[32] Accrual dates were obtained from Shak, 1999[33])	March 1993–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,[24] Roche report,[8] and an abstract published by Cobleigh, 1999.[34] Information (QoL data) on the study was also presented in Osoba and Burchmore, 1999[29] and in an abstract by Lieberman *et al.*, 1999.[35] Interim results were presented in an abstract by Cobleigh *et al.*, 1998[36])	April 1995 and September 1996	222	Second or third line	All participants received trastuzumab	None
Study H0650g (published paper by Vogel *et al.*[25] Information on this study was also presented as an abstract (Vogel *et al.*, 2000[37]). However, the results in the two publications differed and, therefore, only information from the published paper[25] is used in the review. Accrual dates were obtained from Shak, 1999[33])	October 1995–May 1998	113	First line	Trastuzumab at a standard lower-dose regimen	Trastuzumab at a higher-dose regimen

(study H0551g[18] and study H0649g[24]) and one RCT (study H0650g[25]), where trastuzumab was administered in both intervention groups.

Two studies (H0551g[18] and H0650g[25]) included women with MBC and one study (H0649g[24]) examined women with ABC. All three studies included women whose breast cancer overexpressed HER2 at level 2+ or 3+ as determined by IHC. There were 39 of 46 (85%) participants who had a tumour overexpressing HER2 at level 3+ in study H0551g,[18] 172 of 222 (77%) in study H0649g[24] and 85 of 113 (75%) in study H0650g.[25]

Two studies included participants who had received previous treatment with an anthracycline and/or taxane. Study H0649g included 201 (94%) women who had been pretreated with anthracycline and 143 (67%) women who had previously received taxane therapy.[24] Prior adjuvant chemotherapy had been received by 146 (68%) women and 214 (96%) had received prior chemotherapy for MBC. In study H0650g, 62 (55%) women had received previous anthracycline therapy and 76 (68%) women had received prior adjuvant chemotherapy.[25] Baselga and colleagues reported that 26 (57%) women had received previous adjuvant chemotherapy, four (8.7%) had received prior neoadjuvant chemotherapy and 38 (83%) had received prior chemotherapy for MBC in study H0551g.[18] It was not stated how many of these women had been pretreated with anthracycline and/or taxane therapy.

In study H0551g, participants received a loading dose of 250 mg of trastuzumab intravenously

followed by 10 weekly doses of 100 mg.[18] Participants with no disease progression at the completion of this treatment period were offered a maintenance dose of 100 mg/week. In study H0649g, the loading dose used was 4 mg/kg followed by a 2 mg/kg maintenance dose.[24] If participants experienced disease progression, the investigators could continue with 2 mg/kg or discontinue treatment. In study H0650g, participants were randomised to receive either trastuzumab at the standard lower-dose regimen of an initial dose of 4 mg/kg followed by 2 mg/kg intravenously weekly (low-dose group (LDG)), or a higher-dose regimen of 8 mg/kg loading and 4 mg/kg weekly until disease progression (high-dose group (HDG)).[25]

The primary endpoint in studies H0649g[24] and H0551g[18] was tumour response, and tumour response and adverse effects in study H0650g.[25]

The duration of follow-up was not stated in one study.[18] The median follow-up in the remaining two studies were 12.8 months (range not given) in study H0649g[24] and 11 months (range 1.2 to 35 months) in study H0650g.[25]

Excluded studies

During the initial searches (for RCTs evaluating the use of trastuzumab alone or in combination with other agents versus systemic therapy without trastuzumab), 19 studies were ordered as full papers and then excluded when the inclusion criteria were applied by two reviewers independently (see appendix 6). Five were non-systematic reviews of treatment for breast cancer,[38–42] one was a report of pooling of safety data from three trials,[30] eight were trials of trastuzumab that did not include a control group,[19,24,34,43–47] two were preclinical trials which did not involve human participants,[48,49] one was an evaluation of changing levels of HER2 in patients treated with paclitaxel[50] and one was not a clinical trial.[51]

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 HER2-overexpressing MBC.[52] The study included tumour response as an outcome measure. However, it was excluded because tumours were considered to overexpress HER2 if ≥ 10% of tumour cells had positive membrane staining (HER2 overexpression at level 2+ indicates that 25–50% of tumour cells have positive staining)[18] and the number of participants with HER2 overexpression at level 3+ was not reported. Thirteen excluded studies were unsystematic reviews investigating the use of trastuzumab for the treatment of breast cancer,[32,53–63] one was a review examining trial design,[64] one was a study investigating the level of HER2 overexpression in a cohort of women with breast cancer,[65] one was a study that compared serum and tissue HER2 overexpression in MBC prior to trastuzumab therapy[66] and one studied the effect of trastuzumab on cellular DNA and cell cycle.[67]

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). However, in one study only 13 of 16 participants had breast cancer and in the second study 14 of 17 had breast cancer. As they were Phase I studies (usually used to determine the dose-related tolerability and safety in humans and drug absorption and distribution pharmacokinetics),[68] the main outcome measures were adverse events and pharmacokinetic data. Although tumour response rates were also reported, this information was not presented according to cancer type, therefore, these studies were excluded.

Quality of included studies

Combination therapy

The quality of the included trastuzumab trial (H0648g)[17] was assessed using the checklist presented in appendix 7.[69] A summary is presented in *Table 3*. Some important information relating to the methodological conduct of the trial submitted by Roche was marked confidential and has, therefore, been removed from this document.

Randomisation

The randomisation procedure used by study H0648g 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.

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 performance 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

TABLE 3 *Quality of the included trastuzumab combination therapy trial (according to the checklist presented in appendix 7)*[*]

Study	Sample size (arms)	Randomisation procedure adequate	Allocation concealed	Number randomised stated	Baseline details	Baseline comparability 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
Slamon *et al.*, 1999[17] (study H0648g)	469 (two)	Yes	Yes	Yes	Partially	No	Yes	No	Partially	No	No	No	Yes	Yes	Yes

[*] *Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable)*

disease-free interval at baseline was also reported. Information relating to the baseline characteristics of participants in the trastuzumab and control groups 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 of the trial was presented in the published paper.[17] 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 during 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.[64] 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 person administrating the treatment nor the patient would have been blind to the treatment allocation.

Responses to treatment were confirmed by an independent Response Evaluation Committee (REC). Members of the REC were blind to treatment group assignment. The REC assessed tumour response in 99% of the 452 patients who had an assessment after baseline evaluation and 95% of the 469 patients who were enrolled in the study. 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 participants from the intervention group were reported to have discontinued on the first day of the trial prior to receiving any treatment. 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. Reasons for discontinuation were presented according to treatment group assignment (marked as commercial in confidence)[8] and all participants were included in the final analysis. At the time of disease progression, participants were allowed to enrol in the follow-on protocol (study H0659g) where all participants were permitted to receive trastuzumab.

ITT analysis
Efficacy analysis was conducted using the ITT approach.

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 dealt with 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.

Monotherapy
The quality of the included trastuzumab monotherapy studies (H0551g,[18] H0650g[25] and H0649g[24]) were assessed using the checklists presented in appendix 7. A summary is presented in *Tables 4* and *5*.

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,

TABLE 4 *Quality of the included trastuzumab monotherapy studies (according to the checklist for case series presented in appendix 7)*[*]

Study	Sample size	Representative sample	Explicit inclusion	Individuals entered the survey at a similar point	Long enough follow-up	Use of objective criteria or blinding to assess outcomes	Sufficient description of the subseries and the distribution of prognostic factors?
Baselga *et al.*, 1996[18] (study H0551g)	46	Yes	Yes	Partially	Unclear	Partially	NA
Cobleigh *et al.*, 1999[24] (study H0649g)	222	Yes	Yes	Partially	Partially	Yes	Yes
Vogel *et al.*, 2001[25] † (study H0650g)	113	Yes	Yes	Unclear	Partially	No	No

[*] *Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable)*

[†] *Study H0650g was an 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*

alternatively, the number of women for whom these treatments were unsuitable.[18] The remaining two studies[24,25] 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.[25] Both studies failed to specify whether these previous therapies had been used in the adjuvant setting or for the treatments of MBC.[24,25]

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 timepoint (i.e. severity of disease and prognosis is similar for selected participants)

All three studies included women with advanced MBC. However, for two studies (H0551g[18] and H0649g[24]), there were slight variations within individual study populations with regards to some baseline characteristics (e.g. number of metastatic sites,[18,24] number of lymph nodes at primary diagnosis[24] and disease-free interval[24]) that relate to the severity or progression of the disease. The disease-free interval was not reported for study H0551g.[18] For study H0650g (an 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.[25] In addition, for each characteristic, only the number and percentage of participants within a subgroup 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 because just over one-quarter of the participants (27%) had a disease-free interval of < 12 months and 30% of the participants had three or more metastatic sites.

Follow-up

The median length of follow-up was 12.8 months (range not stated) for one study (H0649g)[24] and 11 months (range 1.2 to 35 months) in another (study H0650g).[25] The primary endpoint for both studies was tumour 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 trials.[70] The follow-up is, therefore, deemed to be long enough to assess objective tumour response associated with trastuzumab, but the follow-up period may not have been sufficient for assessing long-term patient response (such as survival or time to disease progression), although prognosis is generally poor in patients with MBC. The length of follow-up was not stated for study H0551g.[18]

Use of objective criteria and blinding to assess outcomes

The primary objective in all three studies was to measure tumour response. The definition used to measure complete and partial tumour response was only reported in two studies (H0551g[18]

TABLE 5 *Quality of the included trastuzumab monotherapy trial (according to the checklist for RCTs presented in appendix 7)*[*]

Study	Sample size (arms)	Random-isation procedure adequate	Allocation concealed	Number randomised stated	Baseline details	Baseline compar-ability achieved	Eligibility criteria	Co-interventions stated	Blinding of outcome assessors	Blinding of adminis-trators	Partic-ipants blinded	Success of blinding checked	Follow-up ≥ 80%	Outcomes of with-drawals	ITT
Vogel *et al.*, 2001[25] (study H0650g)	113 (two)	Unclear	Unclear	Yes	No	Unclear	Partially	No	Unclear	Unclear	Yes (to dosage level only)	No	Yes	No	No

[*] *Items were graded in terms of Yes (item properly addressed), No (item not properly addressed), Partially (item partially addressed), Unclear (item unclear or not enough information) or NA (not applicable)*

and H0649g[24]). The investigators, as well as an independent REC composed of an oncologist and a radiologist, assessed these outcomes. The committee was reported to have been blind in study H0649g,[24] but not in study H0551g.[18] Antitumour response was evaluated by the investigators in study H0650g, and no blinding was reported.[25] This means that the intervention measure of tumour response may represent an overestimation, as demonstrated by study H0649g,[24] which reported that although both the investigators and REC identified the same number of complete tumour response, a higher rate of partial tumour response was reported by the investigators (11 versus 17%).

Description of subseries and distribution of prognostic factors

Two studies (H0649g[24] and H0650g[25]) examined 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)[24] and only partially reported in the second (although the total number of participants in each subgroup analysis was identified). The number of subseries analysis undertaken in total was not stated for study H0649g, but the findings of those that were found to be significant were reported (tumours that overexpressed HER2 at level 3+ and participants whose time to first relapse was > 6 months).[24] A multivariate logistic regression analysis was then conducted to investigate whether any of the baseline characteristics were independent predictors of tumour response. Study H0650g was an RCT of trastuzumab administered as two different dosage regimens.[25] 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 were reported, but the number randomised to the different intervention groups was not stated 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 an RCT of trastuzumab administered as two different dosage regimens.[25] The quality of the study, according to the checklist for RCTs, was deemed to be poor. Information relating to most of the checklist criteria was not reported. The method of randomisation was not reported and it was not stated whether or not 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 related to disease progression. The follow-up period was only reported by two studies (H0649g[24] and H0650g[25]). The primary objective in all three studies was to measure tumour response. Follow-up was considered to be long enough to assess objective tumour response associated with trastuzumab, but may not have been sufficient for assessing long-term patient response (such as survival or time to disease progression), even though prognosis is generally poor in patients with MBC. The definition used to measure complete and partial tumour response was only reported in two studies (H0551g[18] and H0649g[24]). The investigators, as well as an REC, assessed these outcomes. The committee was reported to have been blinded in study H0649g[24] but not in study H0551g.[18] Antitumour response was evaluated by only the investigators in study H0650g, and no blinding was reported.[25] Two studies (H0649g[24] and H0650g[25]) undertook a comparisons of subseries, but there was sufficient description of the series and the distribution of prognostic factors in only one study (H0649g).[24] The RCT was considered to be of poor quality when assessed according to the quality checklist for RCTs.[25]

Assessment of effectiveness

Combination therapy

Information on the trial included subgroup analysis relating to the 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 of participants in each subgroup were small and HER2-overexpression level was not specified as a stratification variable for 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 were based on the cut-off date October 1999 (31 months after the enrolment of the last patient, and a median follow-up of 35 months (range 30 to 51).

Tumour response

Some information relating to the outcome tumour response, which was marked as confidential, has been removed from the text.

Complete tumour response was defined as the disappearance of all radiographically and/or visually apparent tumour. Partial tumour response was defined as a reduction of ≤ 50% (but < 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 tumour response. A two-sided χ^2 test was used to compare the overall tumour response rates between the two treatment groups. Progressive disease was defined as an increase of ≥ 25% of any measurable lesion and/or death, and the commencement of other antitumour therapy or discontinuation of treatment were incorporated into the definition of treatment failure.

Both complete and overall tumour responses were achieved in a significantly greater number of participants treated with trastuzumab compared to those treated with chemotherapy alone. The results are presented in *Tables 6* and *7* along with the RRs and 95% CIs.

TABLE 6 *Summary of tumour response for trastuzumab plus chemotherapy*

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

* *The number of participants who had disease progression or treatment failure were marked confidential within the report submitted by Roche*

TABLE 7 *Summary of tumour response for trastuzumab plus paclitaxel*

Outcome	Trastuzumab (*n*/*N*)	Control (*n*/*N*)	RR
Complete response (RR > 1 favours trastuzumab)	7/92	2/96	3.65 (95% CI, 0.89 to 15.22)
Overall tumour response (RR > 1 favours trastuzumab)	38/92	16/96	2.48 (95% CI, 1.49 to 4.12)
Disease progression (RR < 1 favours trastuzumab)*	–	–	0.38 (95% CI, 0.27 to 0.53)
Treatment failure (RR < 1 favours trastuzumab)*	–	–	0.46 (95% CI, 0.33 to 0.63)

* *The number of participants who had disease progression or treatment failure were marked confidential within the report submitted by Roche*

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 statistically significantly greater number of participants treated with chemotherapy alone compared to those who received trastuzumab plus chemotherapy. The results along with RRs and 95% CIs are presented in *Table 6*.

Of participants in the trastuzumab plus paclitaxel treatment group, 8% (7/92) had a complete tumour 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 tumour 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 were also found to be significantly less in participants treated with trastuzumab plus paclitaxel compared to paclitaxel alone.

Duration of tumour response

The results relating to duration of tumour response are presented in *Tables 8* and *9*. Some information relating to the outcome duration of tumour response, which was marked as confidential, has been removed from the text.

Time to disease progression was defined as the time from randomisation until documented disease progression or death (whichever occurred first). Duration of overall tumour response was defined as the time from the initial complete or partial tumour 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.

Kaplan–Meier survival methodology was reported to have been used to estimate the median time to disease progression, and the median time to treatment failure for each treatment group. A two-sided log-rank test was used to compare the two treatment groups. 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 HR was not given and insufficient information was presented to calculate the HR or any measure of its variance. The Kaplan–Meier plot of time to disease progression was presented.

The addition of trastuzumab was reported to have significantly increased the median duration of tumour response from 6.1 months (95% CI, 5.5 to 7.8) to 9.1 months (95% CI, 7.7 to 11.0; $p < 0.001$). However, no HR was presented and insufficient information was provided to calculate it. The median duration of tumour response for participants treated with trastuzumab plus paclitaxel was over twice that of participants treated with paclitaxel alone ($p < 0.001$, using the log-rank test).

TABLE 8 *Summary of duration of tumour response (months) for trastuzumab plus chemotherapy*

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

TABLE 9 *Summary of duration of tumour response (months) for trastuzumab plus paclitaxel*

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

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 HR. 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 ($p < 0.001$).

As seen from *Table 9,* 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).

Survival

The results relating to survival data are presented in *Tables 10–14*. Some information relating to survival, which was submitted as confidential, has been removed.

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 with the trastuzumab combination compared to chemotherapy alone ($p = 0.046$). Kaplan–Meier curves of overall survival were presented but the HR was not reported.

Of participants in the paclitaxel alone group, 72% (69/96) 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 *Tables 13* and *14*.

TABLE 10 *Summary of survival (months) for trastuzumab plus chemotherapy. (The results of the subgroup analysis relating to HER2 overexpression at levels 3+ and 2+ were designated as confidential and have, therefore, been removed)*

Outcome	Trastuzumab		Control		*p*-value reported by authors
	N	Median	*N*	Median	
Median survival time	235	25.1 (95% CI, 22.2 to 29.5)	234	20.3 (95% CI, 16.8 to 24.2)	0.046

TABLE 11 *Summary of mortality rates at 1 year for trastuzumab plus chemotherapy*

Outcome	Trastuzumab rate (%) (HER2 3+ *n* = 176, HER2 2+ *n* = 59)	Control rate (%) (HER2 3+ *n* = 173, HER2 2+ *n* = 61)	Summary statistic value[†]
Survival at 1 year	79.1	68.4	$p < 0.05$
1-year mortality rates (data cut-off = 31 December 1997)[*]	–	–	–
Enrolled patients who were alive (data cut-off = October 1999)[*]	–	–	RR of death = 0.80 (95% CI, 0.64 to 1.00)
Enrolled patients who were alive for HER2 overexpression at level 3+[*]	–	–	–
Enrolled patients who were alive for HER2 overexpression at level 2+[*]	–	–	–

[*] *The results relating to the 1-year mortality rates and the number of participants who were alive (including subgroup analysis), were marked confidential within the report submitted by Roche and have, therefore, been removed from this document*
[†] *CIs were computed using the normal approximation to binomial distribution and* p*-values were based on Pearson's chi-square*

TABLE 12 *Summary of patient deaths for trastuzumab plus chemotherapy. (Information relating to this table was made available to NICE, but was designated as confidential and has, therefore, been removed from this document)*

TABLE 13 *Summary of survival (months) for trastuzumab plus paclitaxel*

Outcome	Trastuzumab plus paclitaxel		Control		*p*-value reported by authors
	N	Median	*N*	Median	
Median survival time	92	22.1 (95% CI, 16.9 to 28.6)	96	18.4 (95% CI, 12.7 to 24.4)	0.17

TABLE 14 *Summary of mortality rates at 1 year for trastuzumab plus paclitaxel*

Outcome	Trastuzumab rate (%) (*n* = 92)	Control rate (%) (*n* = 96)	RR
Enrolled patients who were alive (data cut-off = October 1999)*	–	–	RR of death = 0.80 (95% CI, 0.56 to 1.11)
Survival at 1 year	72.8	61.5	–
1-year mortality rates (data cut-off = 31 December 1997)*	–	–	–

* *The results relating to the 1-year mortality rates and the number of participants who were alive were marked confidential within the report submitted by Roche and have, therefore, been removed from this document*

Toxicity

Some information relating to the outcome toxicity, which was marked as confidential, has been removed from the text.

As seen from *Table 15*, 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 > 10% of the participants. Severe heart failure occurred in a greater number of participants treated with chemotherapy plus trastuzumab than those treated with chemotherapy alone (10 versus 2%). More participants treated with trastuzumab plus chemotherapy (8%) had a fever or pharyngitis than those in the control group (4%), and fewer participants treated with trastuzumab plus chemotherapy (26%) had alopecia compared to those treated with chemotherapy alone (35%).

As seen from *Table 16*, there were no significant differences between paclitaxel plus trastuzumab and paclitaxel alone for any severe adverse events as reported by > 10% of the participants.

Twenty-five participants (19 in the subgroup given an anthracycline plus cyclophosphamide plus trastuzumab and six 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 three 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.[17]

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 (*Table 17*). The committee was composed of two oncologists and one cardiologist.[64]

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*).

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 appeared to increase the incidence of cardiac dysfunction.

TABLE 15 *Severe adverse events (that occurred in > 10% of participants*) for trastuzumab plus chemotherapy*

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

* *Excludes five participants who were never treated*

QoL

Health-related QoL (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 (version 1.0) with the breast cancer module (BR-23) at baseline and at weeks 8, 20, and 32. Five prospectively defined domains (physical, role, social, global QoL 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 by the analysis of variance method using the last observation carried forward (death was assigned a value of 0). Missing data at weeks 8 or 10 were not included in the analysis.

TABLE 16 *Severe adverse events (that occurred in > 10% of participants) for trastuzumab plus paclitaxel*

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

TABLE 17 *Incidence of CREC diagnosed cardiac dysfunction for trastuzumab plus chemotherapy. (Information relating to this table was made available to NICE, but was designated as confidential and has, therefore, been removed from this document)*

At baseline, 431 of 469 (92%) participants completed the questionnaire. At subsequent timepoints, 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.[29] By week 32, there were trends for improvement in all five primary, as well as secondary, domains (*Table 19*). 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.[30] The results may have been influenced by the fact that the analysis used the 'last observation carried

TABLE 18 *Overview of cardiac events incidence in study H0648g*[17]

Classification of event according to likely aetiology*	Trastuzumab plus paclitaxel (*n*/*N* (%))	Paclitaxel (*n*/*N* (%))	*p* (χ^2)	Trastuzumab plus anthracycline chemotherapy (*n*/*N* (%))	Anthracycline chemotherapy (*n*/*N* (%))	*p* (χ^2)
Symptomatic heart failure 'anthracycline typical'	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	4/91 (4.4%)	7/95 (7.4%)	0.390	8/143 (5.6%)	8/135 (5.9%)	0.906

* *Categories are mutually exclusive*

TABLE 19 *QoL with trastuzumab plus chemotherapy*

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

SE, standard error

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

forward' method. In patients with progressive disease, this approach tends to overestimate the results at the missing timepoints, since the scores from the completions at earlier timepoints in the study, before disease progression, are likely to be better (i.e. higher functioning scores and lower symptom scores) than those from later timepoints at which data are more likely to be missing.[29]

Monotherapy

Trastuzumab is currently licensed for the treatment of MBC overexpressing HER2 at the IHC level 3+. All three studies included women with MBC over-expressing HER2 at levels 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.[18] The median follow-up in the remaining two studies included 12.8 months (range not given) in study H0649g[24] and 11 months (range 1.2 to 35 months) in study H0650g.[25]

Tumour response

The definitions used to measure tumour response were presented for two studies (H0551g[18] and H0649g[24]). Complete tumour response was defined as the disappearance of radiographically, palpable and/or visually apparent tumour. Partial tumour 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.

All tumour response outcomes (partial and complete) were measured by the investigators[18,24,25] and confirmed by an independent REC in two studies (H0551g[18] and H0649g[24]), which were reported by Cobleigh and colleagues to have been blind.[24] The tumour response rates reported in the current review include those assessed according to the REC for two studies (H0551g[18] and H0649g[24]) and according to the investigators for study H0650g.[25] Stable and progressive disease were assessed by the investigators in all three studies. *Table 20* summarises the data for tumour response, and data on stable and progressive disease are presented in *Table 21*.

The primary objective for all three studies was to measure overall tumour response rate, which

TABLE 20 *Summary of tumour response for trastuzumab monotherapy*

Study	All participants (*n*/*N* (%))	HER2 overexpressors at level 3+
Complete response		
H0551g[18]	1/43 (2%)	–
H0649g[24]	8/222 (4%)	5/172 (3%)
H0650g[25] (LDG)*	2/58 (3%)	–
H0650g[25] (HDG)*	4/54 (7%)	–
Partial response		
H0551g[18]	4/43 (9%)	–
H0649g[24]	26/222 (12%)	26/172 (15%)
H0650g[25] (LDG)*	12/58 (21%)	–
H0650g[25] (HDG)*	8/54 (15%)	–
Overall response		
H0551g[18]	5/43 (11.6%, 95% CI, 4.36 to 25.9)	–
H0649g[24]	34/222 (15%, 95% CI, 11 to 21)	31/172 (18%, 95% CI, 12.6 to 24.6)
H0650g[25] (LDG)*	14/58 (24%, 95% CI, 13 to 35)	26/85 (31%; both groups combined)
H0650g[25] (HDG)*	12/54 (15%, 95% CI, 11 to 33)	–

* *Study H0650g[25] was an 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 (HDG)*

TABLE 21 *Summary of stable and progressive disease for trastuzumab monotherapy*

Outcome	Study H0551g[18]	Study H0649g[24]	Study H0650g[25] (LDG)*	Study H0650g[25] (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 H0650g[25] was an 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 (HDG)*

ranged from 12% (study H0551g)[18] to 24% (study H0650g, for participants randomised to the LDG).[25] Only two studies reported on the overall tumour response rate for individuals with MBC overexpressing HER2 at level 3+, which ranged from 18% (H0649g)[24] to 31% (H0650g, for both treatment groups combined).[25] 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 tumour response ranged from 2% (H0551g)[18] to 7% (H0650g, for participants randomised to the HDG)[25] and partial response ranged from 9% (H0551g)[18] to 21% (H0650g, for participants randomised to the LDG)[25] of participants. Only one study (H0649g) reported the number of participants with MBC overexpressing HER2 at level 3+ who showed complete or partial tumour response, which included 5 (3%) and 26 (15%), respectively.[24]

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)[25] to 14 (33% in study H0551g).[18] Disease progression was reported by two studies and was seen in 22 (51% in study H0551g)[18] and 93 (44% in study H0649g)[24] participants. Neither stable nor progressive disease was reported according to the level of HER2 overexpression in any study.

Duration of tumour response

The duration of tumour response is presented in *Table 22*. In study H0650g, the data for the two intervention groups were only presented combined.[25] Two studies reported fairly similar

TABLE 22 *Summary of duration of tumour response (months) for trastuzumab monotherapy*

Outcome	Study H0551g[18]	Study H0649g[24]	Study H0650g[25] *
Median duration of overall response	–	9.1 (range 1.6–> 26; *n* = 34) *HER2 overexpression at level 3+*: 9.1 (range 5.6–10.3; *n* = 172)	9.0 (*n* = 16)
Median time to treatment failure	–	2.4 (range 0–> 28)	
Median time to disease progression	–	3.1 (range 0–> 28; *n* = 213)	3.4 (*n* = 113)
	For participants with minor response or stable disease: 5.1 (*n* = 16)	*HER2 overexpression at level 3+*: 3.2 (range 2.6–3.5; *n* = 172)	*For participants with overall response*: 8.0 (*n* = 26) *For participants with stable disease at > 6 months*: 10.8

* *Study H0650g[25] was an RCT where participants were randomised to receive trastuzumab at one of two dosage regimens. Data reported on duration of tumour response were for both groups combined*

duration of overall tumour response and median time to disease progression (9.1 and 3.1 months, respectively, in study H0649g[24] and 9.0 and 3.4 months in study H0650g).[25]

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.[24] Study H0650g reported that for participants with an overall tumour response, time to treatment failure was 8 months and for those with stable disease for > 6 months it was 10.8 months.[25] 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.[18]

One study (H0649g) reported the median duration of tumour response for participants whose tumours overexpressed HER2 at level 3+ as 9.1 months (range 5.6–10.3).[24] The same study reported that the median time to disease progression in this group was 3.2 months (range 2.6–3.5).

Survival

Survival data are presented in *Table 23*. Two studies reported data on survival endpoints (H0649g[24] and H0650g[25]). One study (H0649g) reported that the median survival time using Kaplan–Meier methodology was 13 months (range 0.5–30).[24] 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.[25]

Toxicity

The number of reported severe (grade 3 or 4) adverse events are presented in *Table 24*. For one study (H0649g),[24] with the exception of

TABLE 23 *Summary of survival (months) for trastuzumab monotherapy*

Outcome	Study H0649g[24]	Study H0650g[25] *
Median duration of survival	13 (range 0.5–30; *n* = 222) HER2 overexpression at level 3+: 16.4 (range 12.3–upper limit not reached; *n* = 172)	Range 1.2–35.3 (67% of participants)

* *Study H0650g[25] was an RCT where participants were randomised to receive trastuzumab at one of two dosage regimens. Data reported on survival were for both groups combined*

TABLE 24 *Severe adverse events (grade 3 or 4) for trastuzumab monotherapy*

Adverse event	Study H0551g[18] (*n* = 46)	Study H0649g[24] (*n* = 213)	Study H0650g[25] (LDG, *n* = 58)*	Study H0650g[25] (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
Haematological and lymphatic systems				
Leukopenia	–	3	–	–
Neutropenia	–	2	–	–
Thrombocytopenia	–	2	–	–
Decreased haemoglobin	–	1	–	–
Respiratory tract				
Increased coughing	–	1	–	–
Dyspnoea	–	10	–	–
Hepatic laboratory abnormalites				
Elevated alkaline phosphatase	–	17	–	–
Aspartate aminotransferase	–	13	–	–
Alanine aminotransferase	–	5	–	–
Total bilirubin	–	2	–	–

* *Study H0650g[25] was an 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 (HDG)*

data on laboratory abnormalities, this information represents adverse events that occurred in > 10% of the 213 participants who were treated with at least one dose of trastuzumab.

A blinded independent CREC was established retrospectively to assess cardiac dysfunction in all trastuzumab clinical trials. An overview of the incidence of cardiac events reported by two studies (H0649g[24] and H0650g)[25] 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.[18] 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.[32]

In study H0649g, the most common adverse events that were reported by approximately 40% of patients were infusion-associated fever and/or

TABLE 25 *Overview of the incidence of CREC diagnosed cardiac events for trastuzumab monotherapy*

Classification of event according to likely aetiology*	Study H0649g[24] (trastuzumab alone; *n* = 213/222)	Study H0551g[32] (trastuzumab alone; *n* = 46)	Study H0650g[25] (trastuzumab alone; *n* = 112/113)
Symptomatic heart failure 'anthracycline typical'	14 (6.6%)	Three cardiac dysfunction† (two deaths due to cardiac dysfunction)	One cardiac dysfunction† (likely aetiology not stated)
Definitive cardiac diagnosis other than heart failure	5 (2.3%)		

* *Categories are mutually exclusive*
† *Cardiac dysfunction was manifested as congestive heart failure, cardiomyopathy and/or a decrease in ejection fraction of > 10%*

chills that usually occurred during the first infusion only.[24] The most clinically significant adverse event was cardiac dysfunction, which occurred in ten patients (4.7%). Only 1% of patients discontinued due to treatment-related adverse events.

Adverse events in study H0650g were mainly mild to moderate in nature and occurred more frequently among participants treated with trastuzumab at a higher dose regimen.[25] 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 leukopenia ($n = 1$). Only one participant had cardiac dysfunction (cardiac symptoms or asymptotic decrease (> 10%) in ejection fraction) according to the independent CREC.

Summary of the data on the effectiveness of trastuzumab

The findings of included studies are presented in *Tables 26* and *27*.

Combination therapy

The addition of trastuzumab to chemotherapy resulted in significantly less disease progression and treatment failure. Both complete and overall tumour response were also found to be significantly greater in participants treated with trastuzumab plus chemotherapy compared to those in the chemotherapy alone treatment group.

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

TABLE 26 *Summary of the trastuzumab combination therapy findings*

Study (study type, *n*)	Type of therapy	Intervention details	Tumour response	Survival	QoL	Adverse events
Study H0648g[8,26–30] (RCT, *n* = 469)	First line	Trastuzumab plus chemotherapy versus chemotherapy alone (chemotherapy = anthracycline plus cyclophosphamide or paclitaxel)	Significant differences in favour of trastuzumab in progressive disease, treatment failure and overall response No difference between groups in complete response	Progression-free survival significantly greater in trastuzumab group Overall survival was significantly longer in trastuzumab group, and, of those who entered follow-up trial, there were 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 (study type, *n*)	Type of therapy	Intervention details	Tumour response	Duration of tumour response	Survival	Adverse events
Study H0551g[18] (case series, *n* = 46)	Not stated (82.6% had received prior chemo-therapy for MBC)	Trastuzumab at a loading dose of 250 mg i.v., then 10 weekly doses of 100 mg	*Overall response*: 12% (95% CI, 4 to 26) *Complete response*: 2% *Partial response*: 9%			Toxicity was minimal
Study H0649g[24,29] (case series, *n* = 222)	Second or third line	Trastuzumab at a loading dose of 4 mg/kg i.v., followed by a maintenance dose of 2 mg/kg at weekly intervals	*Overall response*: 15% (95% CI, 11 to 21) *Overall response for HER2 overexpression at level 3+*: 18% *Complete response*: 4% *Complete response for HER2 over-expression at level 3+*: 3% *Partial response*: 12% *Partial response for HER2 over-expression at level 3+*: 15%	*Median duration of overall response*: 9.1 months (range 1.6–> 26)	*Median duration of survival*: 13 months	The most common adverse events, which occurred in approximately 40% of participants, were 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[25,37] (RCT – trastuzumab given to both intervention groups as different regimens, *n* = 113 – LDG *n* = 58 and HDG *n* = 54)	First line	Trastuzumab at a standard lower dose regimen (LDG): loading dose of 4 mg/kg i.v., followed by a maintenance dose of 2 mg/kg at weekly intervals Trastuzumab at a higher dose regimen (HDG): loading dose of 8 mg/kg i.v., followed by a maintenance dose of 4 mg/kg at weekly intervals	*Overall response in the LDG*: 24% (95% CI, 13 to 35) *Complete response in the LDG*: 3% *Partial response in the LDG*: 21% *Overall response in the HDG*: 15% (95% CI, 11 to 33) *Complete response in the HDG*: 7% *Partial response in the HDG*: 15% *Overall response for HER2 over-expression at level 3+ in the HDG and LDG combined*: 31%	*Median duration of overall response*: 9 months	*Survival range*: 1.2–> 35.3 months	Adverse events were mainly mild to moderate, occurring more frequently in the HDG One participant had cardiac dysfunction

i.v., intravenous/intravenously

was presented to calculate the HRs for either outcome measure. (Information relating to the results of a subgroup analysis was marked as confidential and has, therefore, been removed from this document.)

There was no significant difference between the two groups with regard to any of the primary domains for HRQoL. 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 than among 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 overexpressing 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 tumour response (partial and complete), which, according to the three studies, ranged from 12[18] to 24%.[25] An independent tumour response committee assessed tumour response outcomes in two studies, which identified one (2%) complete tumour response and four (9%) partial tumour responses in study H0551g[18] and eight (4%) complete and 26 (12%) partial tumour responses in study H0649g.[24] Tumour response was assessed by the investigators in study H0650g, which reported two (3%) complete and 12 (21%) partial tumour responses among those treated in the LDG and four (7%) complete and eight (15%) partial tumour responses among participants in the HDG.[25] Similar duration of tumour response was reported by two studies ranging from 9 (H0650g)[33] to 9.1 months (H0649g).[24]

Only one study (H0649g) reported the number of complete or partial tumour responses for participants with tumours overexpressing HER2 at level 3+, which were five (3%) and 26 (15%) respectively.[24] In study H0650g, the overall tumour response rate for this group of participants was reported for both treatment groups combined and was 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 endpoints (H0649g[24] and H0650g[25]). One study (H0649g) reported that the overall median survival time using Kaplan–Meier methodology was 13 months (range 0.5–30), and that for participants with tumours overexpressing HER2 at level 3+ was 16.4 months.[24] 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.[25]

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 as monotherapy, and, therefore, an RCT needs to be considered to fully establish whether it has more disbenefits than benefits.

Chapter 4

Discussion and conclusions

Main results

Combination therapy

There was only one included trial of trastuzumab plus chemotherapy (cyclophosphamide plus anthracycline or paclitaxel) versus chemotherapy alone.[17] The study population included women with HER2-overexpressing MBC at level 2+ or 3+ who had not received prior treatment for MBC. The median duration of follow-up was 35 months (range 30 to 51 months). The overall quality of the included trial was considered to be good.

The addition of trastuzumab to chemotherapy resulted in significantly less disease progression and treatment failure and greater complete and overall tumour response when compared to chemotherapy alone. 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. (Information relating to the results of a subgroup analysis was marked as confidential and has, therefore, been removed from this document)

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 case series, H0649g[24] (n = 222) and H0551g[18] (n = 46) and one study (H0650g[25]) was an RCT (n = 113) that randomised participants to receive trastuzumab at a standard low-dose regimen or at a higher dosage level.

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 (H0649g and H0650g).[24,25] The median follow-up was only reported in two studies and ranged from 11 months (H0650g[25]) to 12.8 months (H0649g[24]). The duration of follow-up was considered to be sufficient to demonstrate objective tumour response associated with trastuzumab, but may not have been long enough to assess long-term patient tumour response (such as survival or time to disease progression). However, the prognosis is generally poor in patients with MBC, and the reported median survival for patients with HER2-positive MBC is 9–12 months.

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 checklist for RCTs.

The three studies differed in many respects and, therefore, the results may not be comparable. One study included women who had received extensive prior treatment for MBC (H0649g[24]), whilst a second study (H0650g[25]) used trastuzumab as first-line therapy for MBC. The final study did not report the type of therapy that was used.[18] The dosage regimen used in study H0551g[18] and one of the treatment arms (HDG) in study H0650g[25] differed to that which is currently used in clinical practice. An independent REC assessed the tumour response outcomes in two studies (H0649g[24] and H0551g[18]) that was reported to have been blinded according to Cobleigh and colleagues. In the third study, the outcomes were assessed by the investigator. For study H0649g, the number of participants that were deemed to have partial tumour response according to the REC was lower than that reported by the investigators.

Trastuzumab as monotherapy was shown to have some antitumour effects in terms of overall tumour response (partial and complete), which ranged from 12% (H0551g[18]) to 24% (H0650g[25]). Complete tumour response ranged from 2% (H0551g[18]) to 7% (H0650g, HDG[25]) and partial tumour response ranged from 9% (H0551g[18]) to 21% (H0650g, LDG[25]). Duration of tumour response was reported by two studies ranging from 9 months (H0650g[25]) to 9.1 months (H0649g[24]).

Only one study (H0649g[24]) reported the number of complete or partial tumour responses for

participants with MBC overexpressing HER2 at level 3+, which were five (3%) and 26 (15%), respectively. For study H0650g, the overall tumour response rate for tumours overexpressing HER2 at level 3+ was reported for both treatment groups combined and was 31% (26/85).[25] This means that the majority of tumour responses were in tumours that overexpressed HER2 at level 3+.

Two studies reported data on survival end-points (H0649g[24] and H0650g[25]). Study H0649g reported the median survival time using Kaplan–Meier methodology as 13 months (range 0.5–30).[24] 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. In 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.[25] Trastuzumab when used as a single agent appears to have a relatively low toxicity level.

Overall findings

Overall, trastuzumab plus chemotherapy appears to be effective (in terms of disease progression, treatment failure and both complete and overall tumour response) when used as second-line therapy for HER2-overexpressing MBC at level 3+ when compared to chemotherapy alone. However, it appears 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 tumour response (partial and complete) which, according to three studies, ranged from 12 to 24%. Only two studies reported data on overall tumour response for participants with tumours overexpressing HER2 at level 3+ and only one study reported using trastuzumab as second- or third-line therapy. The included studies did not compare the use of trastuzumab with an alternative systemic therapy and the findings may, therefore, be subject to bias.

Assumptions, limitations and uncertainties

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 the observed effect could be due to confounding factors, which include the natural course of the disease (i.e. variability in the disease status or the influence of different prognostic factors), extraneous factors (e.g. lifestyle, the use of other medication or placebo effect) 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 unbiased estimate of the effect. In other words, the observed effect will either be due to the intervention or chance (random variation), which 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.[23] It is acknowledged that undertaking an RCT of trastuzumab used as second- 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 not yet proven suggesting an RCT of trastuzumab monotherapy versus no chemotherapy may be justified.

The randomisation procedure was performed and reported adequately in the trastuzumab trial, H650g (according to the industry submission data).[25] 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.[70] Concealment of treatment allocation was also thought to have been adequate in the trastuzumab combination trial. Foreknowledge of group assignments leaves the allocation sequence subject to manipulation by researchers and participants.[70] 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 RCTs and non-randomised controlled trials may produce different results.[71] RCTs that have used an inadequate randomisation procedure or have not clearly demonstrated allocation concealment may overestimate the treatment effect size.[71]

For the RCT of trastuzumab combination therapy (H0648g[17]) and one case series of trastuzumab

monotherapy (H0649g[24]), 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. 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 outcome measures evaluated by the clinician, such as alleviation of symptoms and QoL. Previous research has shown that non-blinded studies can overestimate the treatment effect.[72] 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, although the treatment groups were comparable with regard to most of the other characteristics that were 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, although any bias would be in favour of the control group.

The trastuzumab combination trial included women with MBC overexpressing HER2 at levels 2+ and 3+. For most outcome measures, the participants with HER2 overexpression at level 3+ were not compared to those with level 2+ but to all participants, which included those with HER2 at level 3+. As participants with HER2 at level 3+ (349/469) dominated the total group, it is not possible to draw conclusions about patients with HER2 at level 2+ for any of these outcome measures.

When reporting an RCT with survival-type data the recommended appropriate summary statistics that should be used are the log HR and its variance.[73] For the trastuzumab combination therapy trial, no HR or measure of its variance were reported. However, the analysis relating to median survival and duration of tumour response in the RCT (H0650g[25]) and one case series (H0649g[24]) 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.[23] For the RCT, only the *p*-value of the log-rank test was reported along with the median time to event, and only the median time was given for the case series.

Tumour response is a surrogate outcome measure for assessing the effects of treatment on survival or QoL. As women with MBC have such poor prognosis, tumour shrinkage may alleviate symptoms (especially pain) and improve QoL, which means that information relating to complete or partial tumour response would be important but not independent from QoL. However, alleviation of symptoms was not addressed by most included studies, which is surprising because these outcomes are probably the most important for this patient group. Therefore, as partial tumour response is a surrogate measure for complete tumour response, conclusions about effectiveness should be drawn from the complete tumour response findings. Conclusions should not be drawn on the findings of partial tumour response when used as a surrogate measure unless outcomes relating to symptom relief are also reported or the results of both partial and complete tumour 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.[74] 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 cannot 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. Alternatively, there may be a longer delay in publication of less positive findings.

Further research

The evidence to date from good quality trials indicate that trastuzumab is effective when used in combination with paclitaxel as first-line therapy for HER2-overexpressing MBC (at level 3+) and appears to be associated with cardiotoxicity when used in combination with anthracycline. However, this is based on the findings from subgroup analyses of a single RCT (n = 469). For trastuzumab monotherapy, only evidence from non-controlled studies are available so far. This evidence seems to suggest that it may be effective as second-line or subsequent treatment for HER2-overexpressing MBC (at level 3+). Further research is needed to corroborate these findings. This research should include large well-conducted RCTs. 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 tumour response and survival data. Outcomes assessed should include alleviation of symptoms and pain. The number of participants in the control group who were not randomised to receive trastuzumab but were given it on disease progression should also be clearly reported. When reporting survival data, the log HR 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 3-weekly regimen in the treatment of MBC.[75] 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.[75,76] A large NHS funded trial is required to show whether a 3-weekly regimen is equivocal to a weekly regimen in terms of efficacy.

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 appears to be associated with congestive heart failure when given in combination with anthracyclines.

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 tumour 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.

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Appendix 1

Staging of breast cancer

Simplified Union Internationale Contre le Cancer staging of breast cancer[77]

T (tumour size)	T1	Tumour < 2 cm
	T2	Tumour 2–5 cm
	T3	Tumour > 5 cm
	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 and advanced of stages III and IV.

Stage	**Features**
I	Small tumour (< 2 cm)
II	Tumour > 2 cm but < 5 cm and lymph nodes negative **or** Tumour < 5 cm and lymph nodes positive with no detectable distant metastases
III	Large tumour (> 5 cm) **or** Tumour of any size with invasion of skin or chest wall **or** Associated with positive lymph nodes in the supraclavicular region but with no detectable distant metastases
IV	Tumour of any size and lymph nodes either positive or negative with distant metastases

Appendix 2

Search strategies

Initial search

Scoping search

A rapid appraisal to identify ongoing and completed systematic reviews was undertaken on 3 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)

The search strategy was designed to find RCTs and cost-effectiveness studies and, therefore, used relevant methodological filters. Breast cancer terms and the drug names (trastuzumab/Herceptin) were then added to the filters. The MEDLINE searches covered the date range 1986 to August 2000. The searches were carried out on 5 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?r* 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)

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 5 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?r* 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)

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 7 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?r* 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 <http://edina.ed.ac.uk/biosis/>)

BIOSIS-Web was searched via Edina on the Internet. As this interface only accepts simple search strategies, the RCTs and cost-effectiveness studies filters were not used. A simple search strategy including the drug names (trastuzumab/ Herceptin) and breast cancer terms was used. The resulting references were then checked for duplication against those records already found. The BIOSIS-Web searches covered the date range 1993 to 2000. The searches were carried out on 7 September 2000 and identified 75 records.

(herceptin or trastuzumab) and breast*

ISTP: Web of Science (Internet <http://wos.mimas.ac.uk/>)

The Web of Science interface used to search ISTP only accepts simple search strategies, so the RCTs and cost-effectiveness studies 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 11 September 2000 and identified ten records.

CCTR: Cochrane Library (CD-ROM 2000, issue 3)

The 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 RCTs because the database only consists of controlled trial references. The searches were carried out on 6 September 2000 and identified three 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)

DARE: Cochrane Library (CD-ROM 2000, issue 3)

The DARE was searched at the same time as the CCTR database, using the same strategy (see above). The searches were carried out on 6 September 2000 and identified no records.

NHS EED: Cochrane Library (CD-ROM 2000, issue 3)

The NHS EED was searched at the same time as the CCTR database, using the same strategy (see above). The searches were carried out on 6 September 2000 and identified no records.

National Research Register (CD-ROM, 2000, issue 3)

The National Research Register 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 12 September 2000 and identified four ongoing and six completed 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: United Kingdom Coordinating Committee on Cancer Research Register, National Institute of Health, Current Controlled Trials 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 website was searched for abstracts from their annual conference proceedings. The search strategies 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

United Kingdom Coordinating Committee on Cancer Research Register <http://www.cto.mrc.ac.uk/ukcccr/text_only/search.html>
This site was searched on 14 September 2000 and identified no trials.

National Institute of Health <http://clinicaltrials.gov/ct/gui/c/r>
This site was searched on 14 September 2000 and identified 20 trials.

Current Controlled Trials <http://www.controlled-trials.com/login.cfm?returnto=home_page.cfm>
This site was searched on 14 September 2000 and identified eight trials.

CenterWatch Clinical Trials Listing Service <http://www.centerwatch.com/main.htm>
This site was searched on 14 September 2000 and identified two trials.

National Cancer Institute <http://cancernet.nci.nih.gov/trialsrch.shtml>
This site was searched on 14 September 2000 and identified 19 trials.

American Society of Clinical Oncology <http://www.asco.org/>
This site was searched on 14 September 2000 and identified ten 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, ISTP and the CCTR 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, and 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, ISTP, CCTR and the National Research Register databases and thus remained exactly the same.

Main literature search

The following databases were searched.

MEDLINE: SilverPlatter (CD-ROM)

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 13 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?r* 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)

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 13 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?r* 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 2animal"/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)

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 13 August 2001 and identified 87 records.

#1 explode "breast neoplasms"/all subheadings
#2 (breast* near4 (cancer* or tumo?r* 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 <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 checked for duplication against those records already found. The BIOSIS-Web searches covered the date range 1993 to 2001. The search was carried out on 13 August 2001 and identified 204 records.

(herceptin or trastuzumab) and breast*

ISTP: Web of Science (Internet <http://wos.mimas.ac.uk/>)

The Web of Science interface was used to search 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 13 August 2001 and identified 17 records.

(herceptin or trastuzumab) and breast*

CCTR: Cochrane Library (CD-ROM 2001, issue 3)

The 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 13 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, issue 2)

The National Research Register 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 13 August 2001 and identified three ongoing and ten completed 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, ISTP and the CCTR 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 3

Industry submission data from Roche presented to NICE

Effectiveness data

The submission data were based on two studies. One study (Roche study H0649g[24]) 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 because 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,[17] which was an RCT comparing the efficacy of chemotherapy alone versus chemotherapy in combination with trastuzumab in participants receiving first-line therapy for HER2-overexpressing MBC (n = 469). This trial is included in the review. At disease progression, participants were allowed to enrol in the follow-on protocol (Roche study H0659g), which permitted all participants to receive trastuzumab. The results of the follow-on study were not included in the current NICE review because the study did not meet the inclusion criteria. The submission data included a reference to a published abstract of an RCT of trastuzumab used at different doses conducted by Vogel and colleagues.[37] This trial was excluded from the initial review because 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.

Appendix 4

Trastuzumab combination therapy study included in the review

Data that were marked confidential within the report submitted by Roche has been removed.

Study and design	Participants	Intervention details	Adverse effects/ withdrawals	Comments
Study H0648g Slamon *et al*., 1999[27] (Data also extracted from Norton *et al*., 1999,[78] Slamon *et al*., 1998,[26] Baselga *et al*., 1999,[79] Osoba and Burchmore, 1999,[29] an abstract published in *Oncologist*, 1998[80] and company submission data by Roche)[8] ***Study details*** A multicentre Phase III RCT (Roche study H0648g) ***Method of randomisation*** Randomisation was stratified by type of chemotherapy regimen that patients were receiving ***Objective*** To asses the efficacy of Herceptin (trastuzumab) in combination with chemotherapy as first-line treatment for women with MBC overexpressing HER2 ***Length of follow-up*** The last patient was enrolled on 7 March 1997[33] The final analysis of the primary endpoints was performed 9 months after enrolment of the last patient. Survival was analysed 31 months after	Number of participants = 469. First participant was enrolled 12 June 1995 and the last enrolled 7 March 1997 ***Type of breast cancer*** MBC overexpressing HER2 (at a 2+/3+ level). The number of women that had a tumour overexpressing HER2 at a level of 3+ was 249/469 All patients had tumours that overexpressed HER2 as determined by IHC[64] ***Age*** Overall age range: 25–77 years Age of trastuzumab plus anthracycline-based chemotherapy group: mean = 54 years (range 27–76) Age of trastuzumab plus paclitaxel group: mean = 51 (range 25–77) Age of anthracycline-based chemotherapy group: mean = 54 (range 25–75) Age of paclitaxel group: mean = 51 (range 26–73) ***Inclusion criteria*** MBC, overexpression of the HER2 oncogene (at the 2+ to 3+ level), ability to understand and willingness to give informed consent ***Previous treatment*** **Prior adjuvant chemotherapy** Trastuzumab plus anthracycline-based chemotherapy = 57% Paclitaxel plus trastuzumab = 97% Anthracycline-based chemotherapy = 37% Paclitaxel = 100% **Prior hormonal therapy** Trastuzumab plus anthracycline-based chemotherapy = 142/143 Trastuzumab plus paclitaxel = 89/92 Anthracycline-based chemotherapy = 134/138 Paclitaxel = 95/96	***Type of therapy*** First line (no prior chemotherapy treatment for metastatic disease) ***Intervention*** Chemotherapy and trastuzumab (chemotherapy included either anthracycline (doxorubicin or epirubicin) plus cyclophosphamide or paclitaxel; *n* = 235) Anthracycline-based chemotherapy plus trastuzumab (*n* = 143) Paclitaxel plus trastuzumab (*n* = 92) **Dosage** Trastuzumab = 4 mg/kg loading, then 2 mg/kg i.v. every week Doxorubicin = 60 mg/m^2 i.v. Epirubicin = 75 mg/m^2 i.v. Cyclophosphamide = 600 mg/m^2 i.v. Paclitaxel = 175 mg/m^2 i.v. over 3 hours given every 3 weeks **Number of cycles** Six for chemotherapy and trastuzumab for duration of trial ***Comparator*** Anthracycline-based chemotherapy alone (*n* = 138) or paclitaxel alone (*n* = 96). Total *n* = 234 **Dosage** Doxorubicin = 60 mg/m^2 i.v. Epirubicin = 75 mg/m^2 i.v. Cyclophosphamide = 600 mg/m^2 i.v. Paclitaxel = 175 mg/m^2	***Withdrawals*** Five randomised patients discontinued participation in the study before day 1 (assigned to the chemotherapy alone 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) and inadvertent enrolment (*n* = 1) ***Adverse effects*** Trastuzumab was well tolerated except for class III/IV cardiac dysfunction, which was more common with anthracycline-based chemotherapy plus trastuzumab (19%) than with paclitaxel plus trastuzumab (4%) 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 anthracycline-based chemotherapy plus trastuzumab (18% grade 3/4) than with anthracycline-based chemo-	***Author's conclusions*** Addition of trastuzumab to chemotherapy increased the response rate and time to disease progression significantly compared with chemotherapy alone ***Other comments*** Many of the analyses and conclusions are based on subgroup analyses (dependent on the type of chemotherapy that patients received or the level of HER2 overexpression) 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[80] ***Changes to initial trial protocol***[64] – More inclusive eligibility criteria (inclusion criteria broadened and require-

continued

continued

Study and design	Participants	Intervention details	Adverse effects/ withdrawals	Comments
enrolment ended. The median duration of follow-up was 35 months (range 30–51) Responses to treatment were confirmed by an independent REC composed of oncologists and radiologists. The radiographs and/or physical examination findings were evaluated in a blinded manner[64] 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 tumour response rates between the two treatment groups. Kaplan–Meier survival methodology was used to estimate the median duration of tumour 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	**Prior radiotherapy** Trastuzumab plus anthracycline-based chemotherapy = 143/143 Trastuzumab plus paclitaxel = 89/92 Anthracycline-based chemotherapy = 136/138 Paclitaxel = 95/96 ***Other baseline characteristics*** **Level 3+ HER2 overexpression** Trastuzumab plus anthracycline-based chemotherapy = 76% Trastuzumab plus paclitaxel = 74% Anthracycline-based chemotherapy = 70% Paclitaxel = 80% **Karnofsky score between 90–100/60–80** Trastuzumab plus anthracycline-based chemotherapy = 66%/34% Trastuzumab plus paclitaxel = 76%/24% Anthracycline-based chemotherapy = 66%/34% Paclitaxel = 65%/35% **Median number of positive lymph nodes at diagnosis** Trastuzumab plus anthracycline-based chemotherapy = 1.0 Trastuzumab plus paclitaxel = 5.0 Anthracycline-based chemotherapy = 0.5 Paclitaxel = 6.0 **≥ 3 metastatic sites at enrolment** Trastuzumab plus anthracycline-based chemotherapy = 40% Trastuzumab plus paclitaxel = 31% Anthracycline-based chemotherapy = 29% Paclitaxel = 35% **Median disease-free interval (months)** Trastuzumab plus anthracycline-based chemotherapy = 24.5 Trastuzumab plus paclitaxel = 22.4 Anthracycline-based chemotherapy = 22.8 Paclitaxel = 18.9	i.v. every 3 hours given over 3 weeks **Number of cycles** Six of each ***Further information*** All women received chemotherapy prior to randomisation (to trastuzumab therapy). Randomisation was stratified by type of chemotherapy regimen that patients were receiving, which included anthracycline-based chemotherapy to patients having received no prior anthracycline-based chemotherapy (*n* = 281) and paclitaxel to those who had previously received anthracycline-based chemotherapy (*n* = 188) in the adjuvant setting For ethical reasons, at the time of disease progression patients were allowed to enrol into the follow-on protocol H0659g which permitted all patients to receive trastuzumab. Of those in the HER2 overexpression at level 3+ subgroup who were initially randomised to receive paclitaxel alone, 76% underwent a treatment switch to trastuzumab[8] **Subgroup (% getting subsequent trastuzumab)** Anthracycline-based chemotherapy (57%) Anthracycline-based chemotherapy plus trastuzumab (32%) Paclitaxel (74%) Trastuzumab plus paclitaxel (43%)[78]	therapy alone (3%), paclitaxel alone (0%) or paclitaxel plus trastuzumab (2%)[81] The reported incidence of any cardiac dysfunction (which could include dyspnoea, increased coughing, paroxysmal nocturnal dyspnoea, peripheral oedema, S3 gallop and reduced ejection fracture) was 28% in patients treated with trastuzumab plus anthracycline-based chemotherapy and 7% in patients treated with anthracycline-based chemotherapy alone. Patients randomised to paclitaxel plus trastuzumab had a reported 11% incidence of cardiac dysfunction, compared with 1% with paclitaxel alone. Of patients in trastuzumab plus anthracycline-based chemotherapy cohort, 19% developed congestive heart failure of class III/IV severity[82]	ment of histologically confirmed metastases removed) – Simplified study procedures (less tests required and trastuzumab infusion time reduced) – More flexible concomitant chemotherapy – Elimination of placebo infusion

continued

Results		
Outcome 1 (primary endpoint): median time to disease progression (months)	**Outcome 2: treatment failure**	**Outcome 3: median duration of tumour response (months)**
Disease progression was defined as an increase of > 25% in the dimensions of any measurable lesion and was analysed using Kaplan–Meier survival methodology and log-rank test Follow-up time: data cut-off = 31 December 1997 (minimum follow-up of 9 months) **For all participants (ITT)** All chemotherapy plus trastuzumab (7.4, 95% CI, 7.0 to 9.0) versus all chemotherapy alone (4.6, 95% CI, 4.4 to 5.4): $p = 0.0001$ Anthracycline-based chemotherapy plus trastuzumab (7.8, 95% CI, 7.3 to 9.4) versus anthracycline-based chemotherapy alone (6.1, 95% CI, 4.9 to 7.1): $p < 0.05$ Paclitaxel plus trastuzumab (6.9, 95% CI, 5.3 to 9.9) versus paclitaxel alone (2.7): $p < 0.05$ **For participants with HER2 overexpression at level 3+ (*n* = 349)** All chemotherapy plus trastuzumab (7.8) versus all chemotherapy alone (4.6): $p < 0.05$) Anthracycline-based chemotherapy plus trastuzumab (8.1) versus anthracycline-based chemotherapy alone (6.0): $p < 0.05$ Paclitaxel plus trastuzumab (7.1) versus paclitaxel alone (3.0): $p < 0.05$	Time to treatment failure was defined conservatively as disease progression, death, treatment discontinuation for any other reason or initiation of new antitumour therapy **Median time to treatment failure for evaluable participants (months)** All chemotherapy plus trastuzumab (6.9, 95% CI, 6.0 to 7.3) versus all chemotherapy alone (4.5, 95% CI, 4.3 to 4.9): $p = 0.0001$ Anthracycline-based chemotherapy plus trastuzumab (7.2, 95% CI, 6.2 to 7.8) versus anthracycline-based chemotherapy alone (5.6, 95% CI, 4.6 to 6.4): $p = 0.0014$ Paclitaxel plus trastuzumab (5.8, 95% CI, 4.4 to 7.1) versus paclitaxel alone (2.9, 95% CI, 2.0 to 4.3): $p = 0.0001$	Duration of major tumour response (complete or partial response sustained for ≥ 4 weeks) was defined as the time from the initial complete or partial tumour response to documented disease progression or death (whichever occurred first) Follow-up time: data cut-off = 31 December 1997 (minimum follow-up of 9 months). Patients were evaluated for tumour response at weeks 8 and 20 and then at 12-week intervals **For all participants (ITT)** All chemotherapy plus trastuzumab (9.1, 95% CI, 7.7 to 11.0) versus all chemotherapy alone (6.1, 95% CI, 5.5 to 7.8): $p < 0.05$ Anthracycline-based chemotherapy plus trastuzumab (9.1, 95% CI, 7.4 to 12.2) versus anthracycline-based chemotherapy alone (6.7, 95% CI, 5.8 to 8.2): $p < 0.05$ Paclitaxel plus trastuzumab (10.5, 95% CI, 7.3 to 12.5) versus paclitaxel alone (4.5, 95% CI, 3.9 to 6.4): $p < 0.05$ **For participants with HER2 over-expression at level 3+ (*n* = 349)** All chemotherapy plus trastuzumab = 10.0 All chemotherapy alone = 5.6 Anthracycline-based chemotherapy plus trastuzumab = 9.3 Anthracycline-based chemotherapy alone = 5.9 Paclitaxel plus trastuzumab = 10.9 Paclitaxel alone = 4.6

continued

Results contd		
Outcome 4: survival at 1 year	**Outcome 5: overall survival**	**Outcome 6: complete response**
All chemotherapy plus trastuzumab (79.1%) versus all chemotherapy alone (68.4%): $p < 0.05$ Anthracycline-based chemotherapy plus trastuzumab (83.2%) versus anthracycline-based chemotherapy alone (73.2%): $p < 0.05$ Paclitaxel plus trastuzumab (72.8%) versus paclitaxel alone (61.5%) **1-year mortality rates (ITT)** All chemotherapy plus trastuzumab (20.9%, 95% CI, 15.7 to 26.0) versus all chemotherapy alone (31.6%, 95% CI, 25.7 to 37.6): $p < 0.008$	**For all participants (ITT)** All chemotherapy plus trastuzumab (25) versus all chemotherapy alone (20): $p < 0.05$ Anthracycline-based chemotherapy plus trastuzumab (27) versus anthracycline-based chemotherapy alone (21) Paclitaxel plus trastuzumab (22) versus paclitaxel alone (18) **For participants with HER2 over-expression at level 3+ ($n = 349$)** All chemotherapy plus trastuzumab (29) versus all chemotherapy alone (20): $p < 0.05$ Anthracycline-based chemotherapy plus trastuzumab (31) versus anthracycline-based chemotherapy alone (21): $p < 0.05$ Paclitaxel plus trastuzumab (25) versus paclitaxel alone (18) **Median survival time in months (ITT analysis)** Survival was censored for patients who were alive at data cut-off (October 1999). This calculation included patients in the group given chemotherapy alone who received open-label trastuzumab after the occurrence of disease progression All chemotherapy plus trastuzumab (25.1) versus all chemotherapy alone (20.3): $p = 0.0461$	Complete response was defined as disappearance of all radiographically and/or visually apparent tumour (ITT analysis) Follow-up time: data cut-off = 31 December 1997 (minimum follow-up of 9 months) All chemotherapy plus trastuzumab = 18/235 (8%) Anthracycline-based chemotherapy plus trastuzumab = 11/143 (8%) Paclitaxel plus trastuzumab = 7/92 (8%) All chemotherapy alone = 8/234 (3%) Anthracycline-based chemotherapy alone = 6/138 (4%) Paclitaxel alone = 2/96 (2%)

continued

***Results* contd**

Outcome 7: partial tumour response	**Outcome 8: overall tumour response (ITT analysis)**	**Outcome 9: incidence of CREC diagnosed cardiac dysfunction**
Partial tumour response was defined as a decrease of > 50% in the dimensions of a measurable lesion Follow-up time: data cut-off = 31 December 1997 (minimum follow-up of 9 months) All chemotherapy plus trastuzumab = 100/235 (43%) Anthracycline-based chemotherapy plus trastuzumab = 69/143 (48%) Paclitaxel plus trastuzumab = 31/92 (34%) All chemotherapy alone = 66/234 (28%) Anthracycline-based chemotherapy alone = 52/138 (38%) Paclitaxel alone = 14/96 (15%)	Defined as complete or partial response Follow-up time: data cut-off = 31 December 1997 (minimum follow-up of 9 months) **For all participants (ITT)** All chemotherapy plus trastuzumab (118/235 (50%; 95% CI, 44 to 57)) versus all chemotherapy alone (74/234 (32%; 95% CI, 26 to 38)): $p < 0.001$ Anthracycline-based chemotherapy plus trastuzumab (80/143 (56%; 95% CI, 48 to 64)) versus anthracycline-based chemotherapy (58/138 (42%; 95% CI, 34 to 50)): $p = 0.02$ Paclitaxel plus trastuzumab (38/92 (41%; 95% CI, 31 to 51)) versus paclitaxel alone (16/96 (17%; 95% CI, 9 to 24)): $p < 0.001$ **For participants with HER2 over-expression at level 3+ (n = 349)** All chemotherapy plus trastuzumab = 56% All chemotherapy alone = 31% Anthracycline-based chemotherapy plus trastuzumab = 60% Anthracycline-based chemotherapy alone = 42% Paclitaxel plus trastuzumab = 49% Paclitaxel alone = 17%	For the assessment of this adverse event, the independent, blinded 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[64] Results of HRQoL reported by Baselga *et al.*, 1999[79]

continued

***Results* contd**

Outcome 10: HRQoL	**Changes in HRQoL scores at baseline and week 32[29]**	
HRQoL was assessed using the European Organisation for Research and Treatment of Cancer QLQ-C30 (version 1.0) with the breast cancer module (BR-23) at baseline, and at weeks 8, 20 and 32.[79] At baseline, 431 of 469 (92%) participants completed the questionnaire. At subsequent timepoints, 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[29] For HRQoL, five prospectively defined domains (physical, role, social, global QoL 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 by the analysis of variance method using the last observation carried forward (death was assigned a value of 0). Missing data at weeks 8 or 10 were not included in the analysis	***Baseline mean score (± SE)*** **All chemotherapy plus trastuzumab (*n* = 207)** Global QoL: 59.3 ± 1.8 Physical function: 71.5 ± 1.9 Social function: 68.0 ± 2.1 Role function: 64.6 ± 2.5 Fatigue: 37.6 ± 1.9 **All chemotherapy alone (*n* = 194)** Global QoL: 58.4 ± 1.8 Physical function: 70.6 ± 2.1 Social function: 68.1 ± 2.2 Role function: 66.2 ± 2.7 Fatigue: 36.9 ± 2.0 There was no significant difference between the groups for all five predetermined scales at the level of $p = 0.01$	***Week 32 mean score change (± SE)*** **All chemotherapy plus trastuzumab** *(n = 207):* Global QoL: 1.2 ± 2.0 Physical function: –2.9 ± 2.1* Social function: 0.9 ± 2.2 Role function: –3.2 ± 2.8* Fatigue: 1.1 ± 2.2 **All chemotherapy alone (*n* = 194)** Global QoL: –3.9 ± 2.0* Physical function: –8.0 ± 2.3* Social function: –4.5 ± 2.4* Role function: –9.3 ± 2.9* Fatigue: 6.7 ± 2.1 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-C30 and the systemic therapy side-effects domain of the BR-23, all favouring all chemotherapy plus trastuzumab[79]

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

Appendix 5

Trastuzumab monotherapy studies included in the update

Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
Study H0551g Baselga *et al.*, 1996[18] (data were also obtained from Baselga *et al.*, 1999[31] and cardiac data were obtained from a non-systematic review of trastuzumab studies by Baselga, 2000[32]) ***Study design*** Case series (Phase II) ***Setting*** Not stated ***Objective*** To determine the anti-tumour activity of trastuzumab in patients with HER2-overexpressing MBC, as well as to define further the toxicity and pharmacokinetics of trastuzumab	***Inclusion criteria*** Women with extensive MBC. HER2 over-expression at level 2+ or 3+ confirmed by IHC analysis. All participants had to have measurable disease, a Karnofsky performance status of ≥ 60% and preserved haematological, liver, renal and pulmonary function ***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) ***Patient population*** Women (*n* = 46) with a mean age of 50 years (range 30–65). Of these, 39 (84.8%) had tumours over-expressing HER2 at level 3+ and 16 (34.5%) had ≥ three 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%)	***Intervention*** Trastuzumab at a loading dose of 250 mg i.v., then ten weekly doses of 100 mg. Participants with no disease progression at the completion of this treatment period were offered a maintenance phase of 100 mg/week ***Concurrent treatment*** Not stated ***Duration of follow-up*** Not stated ***Outcome measures*** Tumour response: yes Progression-free survival: no Overall survival: no QoL: no Adverse effects: yes	Data on trastuzumab pharmacokinetics were available for 45 participants and 43 were assessable for treatment response. The reason patients were not assessable for tumour response included bacterial infection of an i.v. 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	All tumour responses were confirmed by an independent extramural REC composed of an oncologist and a radiologist. CIs for tumour response rates were calculated using the exact method for a single proportion Complete tumour response was defined as the disappearance of radiographically, palpable and/or visually apparent tumour. Partial tumour 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 tumour response, patients were required to have at least stable bone lesions to be considered as responders Overall tumour responses were seen in five participants, which included one complete remission and four partial remissions (overall tumour response rate = 11.6%, 95% CI, 4.36 to 25.9). Tumour responses were observed in liver, mediastinum, lymph nodes and chest wall lesions. Minor tumour responses, seen in two participants, and stable disease, which occurred in 14 participants, lasted for a median of 5.1 months. Disease progression was seen in 22 participants Adequate pharmacokinetic levels of trastuzumab were obtained in 90% of patients. Toxicity was minimal and no antibodies against the monoclonal antibody rhuMAb HER2 were detected in any participant. One participant experienced grade 3 (based on modified National Cancer Institute common toxicity criteria) pain at the tumour site Three participants had cardiac dysfunction, two of whom died[32]	***Author's conclusions*** Trastuzumab is well tolerated and clinically active in patients with HER2-overexpressing MBC that have 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 ***Other comments*** The length of follow-up is not reported

Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
Study H0649g Cobleigh *et al.*, 1999[24] (data were also obtained from the Roche report[8] and an abstract by Cobleigh, 1999.[34] Information (QoL data) on the study was also presented in Osoba and Burchmore, 1999[29] and Lieberman *et al.*, 1999.[35] Interim results were presented in as an abstract by Cobleigh *et al.*, 1998[36]) ***Study design*** Case series (Phase II) ***Setting*** Outpatient setting. Multicentre study with 54 centres in the USA, Canada, Belgium, UK, France, Germany and Australia ***Objective*** To determine the overall objective tumour response rate to trastuzumab treatment as a single agent and to further characterise the safety profile of trastuzumab	***Inclusion criteria*** Women with advanced MBC. HER2 overexpression at levels 2+ or 3+ confirmed by IHC analysis ***Exclusion criteria*** Presence of untreated brain metastasis, bone metastases as the only disease site, concomitant malignancy not curatively treated, a Karnofsky performance status < 60%, participants who were pregnant or nursing or patients who had used investigational or unlicensed agents within 30 days ***Patient population*** Women (n = 222) with a mean age of 50 years (range 28–81). Of these, 50 had HER2 overexpression at level 2+, 172 had HER2 overexpression at level 3+, 76 (36%) had ≥ three metastatic sites, 155 (72%) had metastatic involvement of the liver and lung, 86 (40%) had a disease-free interval of > 24 months and 80 (37%) had a disease-free interval of < 12 months. Out of 214 participants, 146 (68%) had received prior adjuvant chemotherapy and 214 had received prior chemotherapy for MBC (69 of whom had only received one regimen and 145 had received ≥ two 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. Prior radiotherapy had been	***Intervention*** Trastuzumab used for second- or third-line therapy. The loading dose was 4 mg/kg i.v., followed by a 2 mg/kg maintenance dose at weekly intervals. If patients developed disease progression, the investigator could continue with 2 mg/kg, increase the dose to 4 mg/kg or discontinue treatment. The median number of infusions was 12 (range 1–96) ***Concurrent treatment*** Additional antitumour therapy was permitted at disease progression. Acetaminophen and/or diphenhydramine were used for infusion-related adverse events ***Duration of follow-up*** Median follow-up was 12.8 months (final analysis 15 months after enrolment of the last patient) ***Outcome measures*** **Primary outcome measure** Tumour response: yes **Secondary outcome measures** Progression-free survival: yes Overall survival: yes QoL: yes Adverse effects: yes	Of 222 patients enrolled, 213 received ≥ one dose of trastuzumab. Nine participants were not treated due to 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 (6%) remained in the study without disease progression and 29 (13%) were continuing treatment after disease progression Chemotherapy was added to trastuzumab in 36 patients after disease progression Six participants (3%) discontinued the study due to adverse events, four before and two after disease progression. One participant developed an anaphylactoid reaction during the first dose, one withdrew from treatment after developing tuberculosis and one withdrew due to atherosclerotic heart disease	Time-to-event endpoints were estimated by Kaplan–Meier survival methodology. The effect of baseline characteristics on tumour response rates was evaluated by the χ^2 test and logistic regression model. The risk factors for time to progression were determined by the Cox proportional hazards regression model. Overall tumour response was determined by a blinded independent REC. Any potential cardiac events were evaluated retrospectively by a blinded independent CREC Complete tumour response was defined as the disappearance of radiographically, palpable and/or visually apparent tumour. Partial tumour 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 According to the CREC, there were eight complete and 26 partial tumour responses. The overall tumour response rate for the ITT population (n = 222) was 15% (95% CI, 11 to 21). Participants whose tumours overexpressed HER2 at level 3+ tended to have higher tumour rates than those with HER2 overexpression at level 2+ (18 versus 6%, p = 0.06) According to the investigators, there were 12 minor tumour responses (6%), 62 participants (29%) with stable disease and 93 (44%) with progressive disease The median duration of overall tumour response (n = 34) was 9.1 months (range 1.6–> 26) The median time to disease progression (n = 213) was 3.1 months (range 0–> 28) and to treatment failure was 2.4 months (range 0–> 28). The median duration of survival (n = 222) was 13 months ***Adverse events*** The most common adverse events, which occurred in approximately 40%	***Author's conclusions*** Trastuzumab administered as a single agent produces durable objective tumour responses and is well tolerated by women with HER2-overexpressing MBC 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 ***Other comments*** This was a non-comparative study and therapeutic effect cannot be determined from this type of study Despite the fact that this was a multicentre study involving 54 different international centres, only 222 participants were enrolled The investigators were not blinded to the fact that the participants had received the intervention. Their measure of tumour response and other outcome measures may, therefore, be biased or represent an overestimation (37 (17%) women had partial tumour response according to the investigators

continued

continued

Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
	received by 151 (71%) and 122 (57%) had received prior hormonal therapy			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 due to treatment-related adverse events Adverse events that occurred in > 10% of 213 patients treated with ≥ one dose of trastuzumab (including those not related to treatment) were 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) and dyspnoea (*n* = 10) ***Laboratory abnormalities*** Nine (4%) of 211 participants experienced grade 3 haematological abnormalities, which were manifested by leukopenia (*n* = 3), neutropenia (*n* = 2), thrombocytopenia (*n* = 3) or decreased haemoglobin (*n* = 1). Twenty (9%) of 212 participants experienced ≥ one grade 3 hepatic laboratory abnormality and seven (3%) experienced ≥ one grade 4 hepatic laboratory abnormality	compared to 26 (11%) according to the REC). A blinded REC was only used to measure the primary endpoint, however, a blinded independent CREC was established retrospectively to assess cardiac dysfunction The median follow-up was 12.3 months, which may be too short to make firm conclusions regarding the durability of tumour response It was reported that tumour response rates were significantly higher among those whose time to first relapse was > 6 months (20 versus 9%, $p = 0.03$). However, the number of participants within each subseries was not reported

Study and design	Participants	Intervention details and outcome measures	Withdrawals	Results	Comments
Study H0650g Vogel *et al.*, 2001[25] (Accrual dates and median duration of response were obtained from Shak, 1999[33]) ***Study design*** Single-blind RCT ***Setting*** Multicentre study involving 19 centres in the USA ***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	***Inclusion criteria*** Women with progressive MBC. HER2 overexpression at levels 2+ or 3+ confirmed by IHC analysis. All participants had to have measurable disease and a Karnofsky performance status ≥ 70% ***Exclusion criteria*** Individuals with bone-only disease ***Patient population*** Women (*n* = 113) with a mean age of 54 years (range 28–86). Of these, 85 (76%) had tumours over-expressing HER2 at level 3+, 34 (30%) had ≥ three metastatic sites and 74 (66%) had metastatic involvement of the liver or lung. Median disease-free interval was 17 months with 30 (27%) participants having a disease-free interval 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%) The two groups were reported to be generally comparable in terms of baseline characteristics, but this information was not presented	***Intervention*** Trastuzumab (used for first-line therapy) at a standard lower dose regimen of 4 mg/kg i.v. loading and 2 mg/kg i.v. weekly until disease progression (LDG, *n* = 58) ***Comparator*** Trastuzumab (used for first-line therapy) at a higher dose regimen of 8 mg/kg i.v. loading and 4 mg/kg i.v. weekly until disease progression (HDG, *n* = 54) ***Concurrent treatment*** None reported ***Duration of follow-up*** Median follow-up was 11 months (range 1.2–35) ***Outcome measures*** **Primary outcome measures** Tumour response: yes Adverse effects: yes **Secondary outcome measures** Progression-free survival: yes Overall survival: yes QoL: no	Data were available for 112 evaluable participants	The investigators evaluated tumour response and safety. Any potential cardiac events were evaluated by an independent CREC In the LDG, there were two complete and 12 partial tumour responses compared to four and eight, respectively, in the HDG. The overall tumour response rates were 14 (24%; 95% CI, 13 to 35) in the LDG and 12 (22%; 95% CI. 11 to 33) in the HDG Four and five participants had stable disease at > 6 months in the LDG and HDG, respectively The overall tumour response rate for participants with HER2 overexpression at level 3+ (*n* = 85) was 26 (31%) The Kaplan–Meier estimate of the median duration of the tumour response was 9 months[33] Overall, the median times to progression were 3.4 and 8 months in those achieving complete and partial responses, respectively. For participants with stable disease at > 6 months, the time to progression 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 Adverse events were mainly mild to moderate in nature. Severe adverse events included asthenia (LDG: *n* = 2; HDG: *n* = 4), chills (LDG: *n* = 0; HDG: *n* = 1), fever (LDG: *n* = 1; HDG: *n* = 0), headache (LDG: *n* = 1; HDG: *n* = 1), diarrhoea (LDG: *n* = 1; HDG: *n* = 3) and vomiting (LDG: *n* = 1; HDG: *n* = 2). One participant had cardiac dysfunction (cardiac symptoms or asymptotic decrease of > 10% in ejection fraction) according to the independent CREC	***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 MBC. Trastuzumab is well tolerated and common chemotherapy-associated adverse events, such as myelosuppression and mucositis, were rare ***Other comments*** This study was also reported as an abstract,[37] however, the results in the two publications differed and, therefore, the information in the abstract was not used. According to Vogel *et al.*, 2000,[37] 114 women were randomised No information is presented on how participants were randomised and the baseline characteristics were not presented according to the randomised treatment groups The investigators were not reported to have been blinded to the fact that the participants had received the intervention. Their measure of tumour response and safety measures may, therefore, be biased or represent an overestimation as demonstrated in study H0649g[24] All participants who had a complete or partial tumour response demonstrated 3+ HER2 overexpression

Appendix 6

Excluded studies

List of excluded studies from the initial searches

To be included in the initial review, studies had to fulfill all of the following criteria.

- The study design had to be an RCT.
- The study must have evaluated trastuzumab (Herceptin) alone or in combination with other agents versus systemic therapy without trastuzumab.
- The study had to include individuals with breast cancer.
- The study had to include one of the following outcome measures: tumour response (including complete and partial response), progression-free survival, overall survival, symptom relief, QoL or adverse effects.

Study	Study design	Intervention	Population	Comments
Anon, 1998[38]	No	Yes	Yes	Non-systematic review
Baselga, 1999[30]	No	Yes	Yes	Analysed safety data taken from three trials
Beuzeboc *et al.*, 1999[39]	No	Yes	Yes	Non-systematic review
Burris *et al.*, 1999[43]	No	Yes	Yes	No comparison group (docetaxel in combination with trastuzumab)
Burris *et al.*, 1999[44]	No	Yes	Yes	No comparison group (docetaxel in combination with trastuzumab)
Burstein *et al.*, 1999[45]	No	Yes	Yes	No comparison group (trastuzumab in combination with vinorelbine)
Chia *et al.*, 2000[48]	No	Yes	No	Laboratory-based data and not human participants
Cobleigh *et al.*, 1999[24]	No	Yes	Yes	No comparison group (trastuzumab monotherapy and thus included in update review)
Cobleigh, 1999[34]	No	Yes	Yes	No comparison group (trastuzumab monotherapy and thus included in update review)
Esteva *et al.*, 1999[46]	No	Yes	Yes	No comparison group (trastuzumab in combination with paclitaxel)
Feldman *et al.*, 2000[21]	No	Yes	Yes	Discussion data
Hortobagyi, 1999[40]	No	No	Yes	Review of docetaxel
Konecny *et al.*, 1999[49]	No	Yes	No	Looked at cell lines not patients
Luftner *et al.*, 1999[50]	No	No	Yes	Evaluation of changing levels of HER2 in patients treated with paclitaxel
McLachlan *et al.*, 1999[51]	No	No	Yes	Not a drug trial
Pegram and Slamon, 1999[47]	No	Yes	Yes	No comparison group (trastuzumab in combination with cisplatin)
Seidman *et al.*, 1999[19]	No	Yes	Yes	No comparison group (trastuzumab in combination with paclitaxel)
Untch *et al.*, 2000[42]	No	Yes	Yes	Non-English language and a non-systematic review
Wong, 1999[41]	No	Yes	Yes	Non-systematic review

List of excluded studies from the update searches

To be included in the update review, studies had to fulfill all of the following criteria.

- The study design had to be a cohort study, case–control study or a case series.
- The study must have evaluated trastuzumab (Herceptin) used as a single agent.
- The study had to include individuals with breast cancer overexpressing HER2 at level 3+.
- The study had to include one of the following outcome measures: tumour response (including complete and partial response), progression-free survival, overall survival, symptom relief, QoL or adverse effects.

Study	Study design	Intervention	Population	Comments
Baselga, 2000[32]	No	Yes	Yes	Non-systematic review
Baselga, 2000[53]	No	Yes	Yes	Non-systematic review
Fleming, 1999[64]	No	Yes	Yes	Non-systematic review that looked at the design of clinical trials
Kish *et al.*, 2001[66]	No	No	Yes	Comparison of serum and tissue HER2 overexpression in MBC prior to trastuzumab therapy
Kute *et al.,* 2000[67]	No	Yes	No	Studied the effect of trastuzumab on cellular DNA and cell cycle
Heinzl, 2000[63]	No	Yes	Yes	Non-systematic review
Hiddemann, 2001[60]	No	Yes	Yes	Review with no primary research
Horton, 2001[54]	No	Yes	Yes	Non-systematic review
Norton *et al.*, 1998[55]	No	Yes	Yes	Non-systematic review
Perez Lopez *et al.*, 2000[56]	No	Yes	Yes	Non-systematic review
Pohlmann, 2000[57]	No	Yes	Yes	Review with no primary research
Roche and Ingle, 1999[65]	No	No	Yes	Tested a cohort of women with breast cancer for HER2 overexpression
Sparano, 2001[58]	No	Yes	Yes	Non-systematic review on cardiac toxicity of trastuzumab
Tokuda *et al.*, 1999[52]	Yes	Yes	No	Phase I study of trastuzumab in patients with HER2-overexpressing MBC. Study was excluded because tumours were considered to overexpress HER2 if ≥ 10% of tumour cells had positive membrane staining (HER2 overexpression at level 2+ means that 25–50% of tumour cells have positive staining)[18] and the number of participants with HER2 overexpression at level 3+ was not reported
Treish *et al.*, 2000[59]	No	Yes	Yes	Non-systematic review that included data on HER2 testing
Wagner, 2000[62]	No	Yes	Yes	Review with no primary research
Wagner, 2000[61]	No	Yes	Yes	Review with no primary research

Appendix 7

Quality checklists

Studies of clinical effectiveness

RCTs were assessed using the following criteria, based on Centre for Reviews and Dissemination Report 4:[69]

(1) Was the method used to assign participants to the treatment groups really random? (Computer generated random numbers and random number tables were accepted as adequate, whilst inadequate approaches included the use of alternation, case record numbers, birth dates or days of the week.)
(2) Was the allocation of treatment concealed? (Concealment was deemed adequate where randomisation was centralised or pharmacy-controlled, or where the following were used: serially numbered containers, on-site computer-based systems where assignment is unreadable until after allocation, other techniques with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches included 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 ITT analysis included?

Case series were assessed according to the following criteria, based on Centre for Reviews and Dissemination Report No. 4:[69]

(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 subseries were 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 (item unclear or not enough information) or NA (not applicable).

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We look forward to hearing from you.

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