NATIONAL BREAST
CANCER CENTRE
Incorporating the
Ovarian Cancer Program

TRASTUZUMAB FOR HER2-POSITIVE BREAST CANCER: A SYSTEMATIC REVIEW

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PREPARED BY THE NHMRC CLINICAL TRIALS CENTRE ON BEHALF OF THE
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BACKGROUND

Breast cancer is the most common registerable cancer among Australian women. In 2002, 12,027 new cases of breast cancer were identified with an age standardised incidence of 117 cases per 100,000 women. Australia's incidence of breast cancer (83.2 per 100,000) was lower than the United States of America (101.1), New Zealand (91.9), the United Kingdom (87.2) and Canada (84.3).[1] The 5-year relative survival rate for Australian women diagnosed with breast cancer during 1992−97 was 84%.[2] In Australia in 2004, 2,641 female deaths were attributed to breast cancer. [1]

The drug trastuzumab is a monoclonal antibody and works by targeting breast cancer cells that overexpress the HER2 protein. Overexpression (or amplification) of the HER2 protein is associated with accelerated cell division. By binding to the protein receptors on these cells, trastuzumab interrupts the growth signal, thereby slowing the growth and spread of tumours. Approximately 20% of breast cancers overexpress the HER2 protein. Amplification of HER2 in breast cancer cells has been correlated with adverse prognostic factors such as large tumour size, high nuclear grade, and decreased expression of estrogen and progesterone hormone receptors.[3] HER2 amplification has also been associated with reduced disease free survival, and overall survival, for women with node positive or node negative disease.[4]

Immunohistochemistry (IHC) techniques (eg the HercepTest®) and in situ hybridisation (including fluorescence in situ hybridisation (FISH)) are established methods used to detect HER2 overexpression.[5] If the results of an IHC test are reported as 0 or 1+, staining is considered negative, 2+ is indeterminate and 3+ is positive. FISH is used to assess and evaluate HER2 gene amplification, and a positive FISH test is rare in IHC 0 or 1+ tumours.[6]

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

OBJECTIVE

To undertake a systematic review of the best available evidence on the use of trastuzumab (Herceptin®) in breast cancer.

TYPES OF STUDIES

- Properly randomised controlled trials:
  - efficacy and short-term toxicity were only to be evaluated based on properly randomised controlled trials
  - prior to commencing the review it was recognised that it may be necessary to obtain additional information on longer term side effects from uncontrolled early phase (I or II) studies.
- Published between January 1990 and December 2005.
- Peer-reviewed articles in English:
  - data from non-peer reviewed articles was to be included if no other information on the issue addressed in those articles is available; appropriate notations regarding the reliability of this data were made.

TYPES OF PARTICIPANTS

- Women with breast cancer:
  - studies categorised according to stage of disease.
- HER2/neu positive:
  - method of ascertainment of HER2 status was documented, if reported.

TYPES OF INTERVENTIONS

INTERVENTION

- Trastuzumab (Herceptin®) containing regimens:
  - trastuzumab as a single agent
  - trastuzumab in combination with other therapies
  - studies categorised according to the manner in which the intervention was given.

COMPARATORS

- All comparators were considered, including:
  - trials comparing regimens containing trastuzumab with those that do not
  - trials comparing different schedules of trastuzumab.

TYPES OF OUTCOMES

PRIMARY OUTCOMES

- Overall survival
- Progression-free survival
- Long-term side effects

OTHER OUTCOMES

- Response
- Toxicity (short-term)
- Fertility

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

The databases described in APPENDICES

APPENDIX *1* were searched to identify existing clinical practice guidelines and systematic reviews. MEDLINE and PREMEDLINE were searched using the very broad terms in Table 1 to identify clinical trials of trastuzumab in breast cancer.

The specialised register of the Cochrane breast cancer group was also searched. This register routinely searches a number of databases for randomised trials, including databases of ongoing trials. Please note that ability to identify ongoing trials is limited given that prospective registration of clinical trials is voluntary.

As it was not expected that any of the identified trials would address the issue of pregnancy or fertility, an additional search was conducted in an attempt to identify information that may contribute to this section of the review. The search strategy in Table 2 was therefore applied, the intention being to identify studies that had investigated the impact of trastuzumab in pregnant women, as well as its impact on fertility.

Table 1. Search for clinical trials of trastuzumab

Database: Ovid MEDLINE(R) <1966 to May Week 3 2006>
Search Strategy:

---

1 herceptin.mp. (775)
2 Trastuzumab.mp. (1776)
3 1 or 2 (1935)
4 exp breast neoplasms/ (139112)
5 3 and 4 (1410)
6 limit 5 to randomised controlled trial (34)
7 limit 5 to controlled clinical trial (1)
8 "Clinical Trial [Publication Type]"/ (447512)
9 Clinical Trials/ (132610)
10 8 or 9 (506340)
11 5 and 10 (367)
12 11 not (6 or 7) (339)
13 limit 12 to yr="1990 - 2006" (339)
14 limit 13 to "review articles" (175)
15 13 not 14 (164)
16 from 15 keep 1-164 (164)

Table 2. Search for information on Trastuzumab and fertility and pregnancy

Database: Ovid MEDLINE(R) <1966 to May Week 2 2006>
Search Strategy:

---

1 exp Reproduction/ (808133)
2 exp Contraception/ (17699)
3 1 and 2 (9596)
4 Antibodies, Monoclonal/ (126828)
5 herceptin.mp. (773)
6 Trastuzumab.mp. (1770)
7 MKC-454.mp. (1)
8 or/4-7 (127280)
9 or/1-2 (816236)
10 8 and 9 (3869)
11 exp Breast Neoplasms/ (139001)
12 10 and 11 (107)

Database: Embase
Search Strategy:

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1 ('reproduction'/exp OR 'reproduction'
2 ('contraception'/exp OR 'contraception')
3 ('monoclonal antibody'/exp OR 'monoclonal antibody
4 ('herceptin'/exp OR 'herceptin')
5 ('Trastuzumab'/exp OR 'Trastuzumab')
6 1 or 2
7 3 or 4
8 6 and 7
9 ('breast cancer'/exp OR 'breast cancer')
10 8 and 9
11 10 AND [english]/lim AND [humans]/lim AND [2002-2006]

METHODS

ASSESSING TRIALS FOR ELIGIBILITY

A copy of the full article for each reference reporting a potentially eligible trial was obtained.

At least two individuals applied the selection criteria (including the quality of randomisation) to each reference identified by the search strategy, masked to the study results. A third reviewer resolved any discrepancies regarding eligibility or quality.

If a trial had not been published, or was ongoing, information was obtained from the trial protocol or the next best available resource.

QUALITY CONTROL AND PEER REVIEW

One experienced reviewer, and one less experienced reviewer, assessed each potentially eligible study for inclusion in the review (according to the eligibility criteria) and quality. A third reviewer resolved discrepancies when they arose.

ANALYSIS

The most complete dataset feasible was assembled. It was decided not to statistically pool the studies owing to issues relating to the completeness of the available data, and the nature of the studies identified. Refer to *Description of studies* for more information.

ASSESSING THE METHODOLOGICAL QUALITY OF THE INCLUDED STUDIES

Each study has been designated a level of evidence as outlined in Table 1. In addition, each randomised trial was reviewed to assess the potential for bias. The issues relating to the quality of randomised controlled trials included:

- concealment of the allocation sequence
- generation of the allocation sequence
- comparability between groups at the baseline
- inclusion of all randomised participants in the analysis.

These issues are addressed for each study in Appendix 2.

EXISTING GUIDELINES

A search of the web sites listed in Appendix 1 resulted in the identification of a number of relevant guidelines and systematic reviews.

GUIDELINES FOR TRASTUZUMAB IN EARLY BREAST CANCER

The most up-to-date guidelines are those produced by Cancer Care Ontario (Canada).[7] The search for trials included in this review was conducted in August 2004. The review addressed the questions outlined below in women with HER2/neu-overexpressing breast cancer.

- Compared with adjuvant or neoadjuvant chemotherapy alone, does trastuzumab in combination improve clinically meaningful outcomes?
- Compared with placebo or observation, does single-agent trastuzumab adjuvant or neoadjuvant therapy improve clinically meaningful outcomes?
- What is the best way to identify women who will benefit from adjuvant or neoadjuvant trastuzumab therapy?
- What are the adverse events associated with adjuvant or neoadjuvant trastuzumab therapy?
- What are the optimal dose, schedule and duration for adjuvant trastuzumab therapy?

The National Cancer Research Institute (NCRI – UK) has developed UK Clinical Guidelines for the Use of Adjuvant Trastuzumab (Herceptin®) with or following chemotherapy in HER2-positive early breast cancer. The methods used to compile these guidelines are not reported.

The National Institute for Clinical Excellence (NICE – UK) is in the process of producing a guideline, a scope for which is available on the NICE web site.

GUIDELINES FOR TRASTUZUMAB IN METASTATIC BREAST CANCER

The most up-to-date guidelines are those produced by Cancer Care Ontario (Canada).[8] The search for trials was conducted in August 2004. The review addressed the questions outlined below.

- Compared with chemotherapy alone, does trastuzumab in combination with chemotherapy improve clinically meaningful outcomes?
- Compared with placebo or observation, does single agent trastuzumab therapy improve clinically meaningful outcomes?
- What is the best way to identify women who will benefit from trastuzumab therapy?
- What are the adverse events associated with trastuzumab therapy?
- What are the optimal dose, schedule and duration for trastuzumab therapy?

Guidance on the use of trastuzumab for the treatment of advanced breast cancer www.nice.org.uk/TA034 has also been produced by the National Institute for Clinical Excellence (NICE) (UK). The guidance was informed by work performed by The National Health Service (NHS) Centre for Reviews and Dissemination. Specifically:

- *A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab and vinorelbine for breast cancer,* February 2001
- *A rapid and systematic review of the clinical effectiveness and cost-effectiveness of trastuzumab for breast cancer,* October 2001.

This guideline would now be considered out of date. A draft scope for an update of this guideline dated 12 January – 10 February 2006 is available on the NICE web site, but the updated guideline itself is not yet available.

The NHS R&D HTA Programme (UK) has also produced the review '*The clinical effectiveness of trastuzumab for breast cancer: a systematic review*'. The review was published in June 2002, and the search applied is not dated. The objective of the review was to evaluate the clinical effectiveness of trastuzumab in the management of advanced breast cancer. This review would now be considered out of date.

DESCRIPTION OF STUDIES

The search strategy described in Table 1 resulted in the identification of 237 citations for potentially eligible studies. Each citation was assessed for eligibility based on the criteria described in the methods section. All randomised trials investigating trastuzumab in breast cancer were included, regardless of the ability to assess the quality of randomisation.

TRASTUZUMAB FOR EARLY BREAST CANCER

Five randomised controlled trials were identified that have published results about trastuzumab for early breast cancer (one neo-adjuvant and four adjuvant trials). An additional five trials are still ongoing, including the BCIRG 006 trial, which reported interim results at the 2006 meeting of the American Society of Clinical Oncology (ASCO) (see *Characteristics of ongoing randomised trials in early and/or locally advanced breast cancer*).[9]

Although all five trials described the method used to generate the sequence of allocation (permuted blocks, minimisation, dynamic allocation), only one mentioned that randomisation was performed centrally for which no detail was provided. It was therefore not possible to assess the adequacy of allocation concealment in any trial.

Another issue influencing the assessment of the trials in early breast cancer was the length of follow-up available. The FinHer trial had the longest follow-up available (median 36 months); however the role of trastuzumab appeared to be a secondary question in this trial.[10] The HERA trial reported a median follow-up of 1 year and gave results for two of the three arms (the third arm involving 2 years of trastuzumab).[11] In June 2006, the HERA investigators presented updated information for the two arms previously reported during the ASCO meeting; interim results of the BCIRG 006 study were also presented.[9,12] Two trials (NSABPB31 and NCCTG-N9831) have reported efficacy results combined in a single paper, the former reporting only on those patients with at least one follow-up evaluation (1736 of 2043 randomised).[13] Given the incomplete nature of the results reported to date, it was not considered appropriate to statistically pool the results of these trials in a meta-analysis. The results for each outcome have been summarised in Tables 3, 4 and 5, and Figure 1. The primary outcome for each of the four adjuvant trials was disease-free (or recurrence-free) survival.

The relatively small trial (n = 42) of trastuzumab in a neoadjuvant setting closed early based on the results of an unscheduled interim analysis for the outcome pathologic complete response (pCR).[14] The analysis was conducted as a result of surgeons noting the high complete response rate. It is possible that the effect detected occurred by chance, given the small sample size and the arguably insufficient p value used.[15] An additional problem is the assumption that the pCR rate will translate into a survival benefit – an outcome not reported for this trial.

TRASTUZUMAB FOR METASTATIC BREAST CANCER

The search resulted in the identification of six randomised controlled trials that have published results about trastuzumab for metastatic breast cancer, with an additional seven trials still ongoing (see Characteristics of included trials in metastatic breast cancer).

It was not possible to ascertain the quality of randomisation for any of the published trials in metastatic breast cancer, as none have reported the methods used to generate the sequence or conceal treatment allocation.

There are no obvious differences in baseline characteristics in the trial reported by Slamon *et al.* that would suggest a problem with randomisation. In the trial M77001, patients in the docetaxel alone arm were more likely to be ER positive and/or PR positive, and less likely to have received prior anthracyclines, than patients in the docetaxel plus trastuzumab arm. Such imbalance could have occurred by chance. Insufficient information was reported in the abstract by Gasparini *et al.* to make any judgement about the quality of this trial.

Three of the trials that have published results compared chemotherapy alone with chemotherapy plus trastuzumab in women with metastatic, HER2 positive breast cancer. The trial first published in full by Slamon *et al.* in 2001 is referred to by many as being the pivotal study in the study of trastuzumab in breast cancer.[16] It is the only trial with the primary efficacy outcome of time to disease progression. The other two trials were smaller and designed to investigate response and short term toxicity.[17, 18] One of these has been reported in abstract form only.[17]

The trial CALGB 9840 started randomising both HER2 positive and negative patients to two schedules of paclitaxel with or without trastuzumab, but ceased recruitment in HER2 positive patients after the release of results from the study by Slamon *et al*.[19] This trial has not reported results for the trastuzumab comparison.

The two remaining trials both compare trastuzumab-containing regimens. The trial BCIRG 007 is investigating the addition of carboplatin to trastuzumab and docetaxel and, to date, has reported results in abstract form only.[20] The trial reported by Vogel *et al.* randomised 114 HER2 positive women to two doses of trastuzumab.[21] Unfortunately, results for most of the outcomes in this trial are not reported by treatment arm.

EARLY PHASE TRIALS OF TRASTUZUMAB

The search described in Table 1 resulted in the identification of 48 uncontrolled phase I and II trials of trastuzumab for breast cancer (see Appendix 4). Four of these trials were in the neoadjuvant setting, and the remainder were in patients with advanced breast cancer.

Information on follow-up was poorly reported in the phase I and II trials, with 31 if the 48 trials not reporting the median follow-up available. The median follow-up period reported by the remaining studies was 26 months or less, with the exception of two studies with median follow-up of 52[22] and 34 months[23] respectively. Neither of these studies reported information on longer term side effects.

To assist in interpretation, the characteristics of the phase I and II studies have been sorted according to the nature of the question being addressed (See Appendix 4).

TRASTUZUMAB AND PREGNANCY AND FERTILITY

A search was conducted in Medline (1990–2005), Pre-Medline and Embase (1990–2006). This identified 122 citations, eight of which were considered relevant to this aspect of the review, and obtained for further appraisal. Three case studies were identified. The remainder were review articles.

RESULTS

RESULTS OF TRASTUZUMAB FOR EARLY BREAST CANCER

The four trials of adjuvant chemotherapy, involving 6983 women, have all reported data on disease-free survival and overall survival. The results reported for each trial are summarised in Tables 3 and 4, and Figure 1. Three of the four trials have reported data on freedom from distant recurrence (see Table 5).

All four trials have reported statistically significant differences in disease-free survival in favour of trastuzumab, with absolute risk reductions ranging from 5.5% to 12.8%. All trials have also reported an improvement in overall survival with the addition of trastuzumab to chemotherapy, although in most trials the difference was of borderline statistical significance. The recent update of the HERA trial suggests a statistically significant advantage in favour of trastuzumab although these data have only been reported in a conference abstract. (Note: Information for BCIRG 006 has been included in Table 3 for completeness)

Table 3. Disease-free survival (early breast cancer)

Trial ID	Events/number randomised	Results
FinHer	Trastuzumab 12/115 No trastuzumab 27/116	HR 0.42 (95% CI 0.21−0.83) p=0.01 ARR 12.84%
HERA (full paper)	Trastuzumab 127/1694 No trastuzumab 220/1693	HR 0.54 (95% CI 0.43−0.67) p<0.0001 ARR 5.50%
HERA (2006 update)	*Trastuzumab 218 / 1703 patients* *No trastuzumab 321 / 1698 patients*	*HR 0.60* *(95% CI 0.50−0.71)* *p<0.0001* ARR 6.10%
NSABP 31 and NCCTG-N9831	Trastuzumab 133/1672 No trastuzumab 261/1679	HR 0.48 (95% CI 0.39−0.59) p<0.0001 ARR 7.59%

Table 4. Disease-free survival (early breast cancer) (cont'd)

Trial ID	Events/number randomised	Results
BCIRG 006	*Trastuzumab (AC-TH) not reported/1074* *No trastuzumab (AC-T) not reported/1073*	*HR 0.49* *(95% CI not reported)* *p<0.0001* *ARR not calculable*
BCIRG 006	*Trastuzumab (TCH) not reported/1075* *No trastuzumab (AC-T) not reported /1073*	*HR 0.61* *(95% CI not reported)* *p<0.001* *ARR not calculable*

A= doxorubicin; C=cyclophosphamide; H=trastuzumab; T=Docetaxel

Table 5. Overall survival (early breast cancer)

Trial ID	Events/number randomised	Results
FinHer	Trastuzumab 6/115 No trastuzumab 14/116	HR 0.41 (95%CI 0.16−1.08) p=0.07 ARR 6.85%
HERA (full paper)	Trastuzumab 29/1694 No trastuzumab 37/1693	HR 0.76 (95%CI 0.47−1.23) p=0.26 ARR 0.47%
HERA (2006 update)	*Trastuzumab 59 / 1703 patients* *No trastuzumab 90 / 1698 patients*	*HR 0.59* *(95%CI 0.43−0.82)* *p=0.0016* *ARR 1.84%*
NSABP 31 and NCCTG-N9831	Trastuzumab 62/1672 No trastuzumab 92/1679	HR 0.67 (95%CI 0.48−0.93) p=0.015 ARR 1.77%

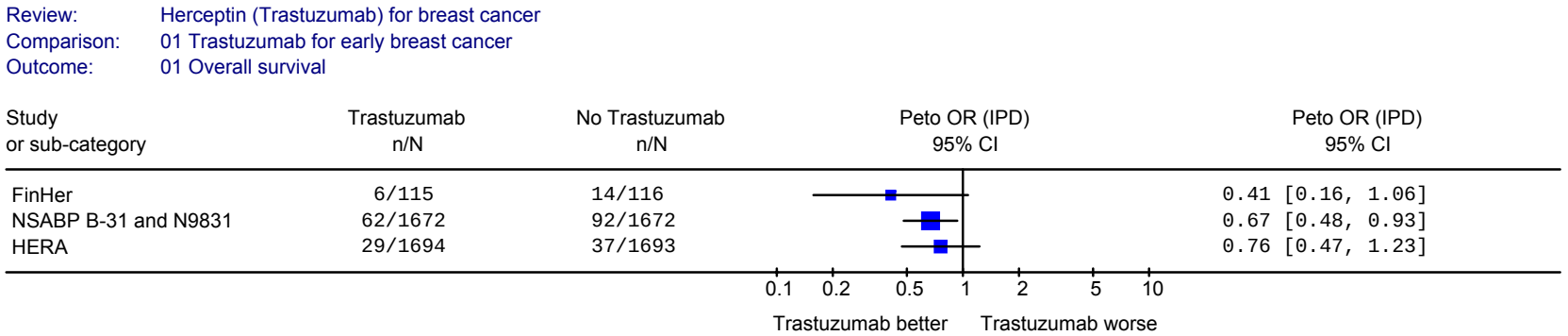
Table 6. Freedom from distant recurrence (early breast cancer)

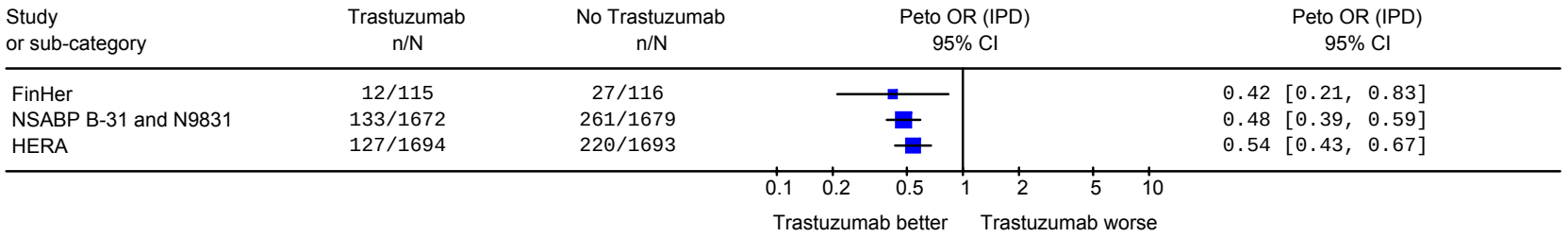
Trial ID	Comparison	Events/number randomised	Results
HERA	Trastuzumab (1 year) v observation in HER2+	Trastuzumab 89/1694 Observation 171/1693	HR 0.49 (95% CI 0.38−0.63) p<0.0001 ARR 4.85%
NSABP 31 and NCCTG-N9831	AC followed by paclitaxel +/− Trastuzumab	Trastuzumab 96/1672 No Trastuzumab 193/1679	HR 0.47, (95% CI 0.37−0.61) p<0.0001 ARR 5.75%

A= doxorubicin; C=cyclophosphamide

Figure 1. Early breast cancer forest plots

Note: these plots are provided to aid in the interpretation of the trial data. No pooled estimate of effect has been calculated.





RESULTS OF TRASTUZUMAB FOR METASTATIC BREAST CANCER

The three trials in metastatic breast cancer investigating the addition of trastuzumab to chemotherapy involve a total of 739 randomised women, although most data is unavailable for the 82 of these patients randomised to the Gasparini trial. The two remaining trials have all reported data on progression-free survival, overall survival and time to treatment failure. The results reported for each trial are summarised in Tables 7−10.

Both trials have reported statistically significant differences in progression-free survival and time to treatment failure in favour of trastuzumab. They have also reported differences of borderline significance in relation to overall survival in favour of trastuzumab.

Table 7. Progression-free survival (metastatic breast cancer)

Trial	Results
Slamon	Median 7.4 months trastuzumab; 4.6 months no trastuzumab, HR not reported; p < 0.001. Relative risk of progression 0.51 (95%CI 0.41−.063)
M77001 (time to disease progression)	Median 11.7 months trastuzumab; 6.1 months no trastuzumab, HR not reported; p = 0.0001
Gasparini (TTP)	*Preliminary*: Median 198 days trastuzumab; 171 days no trastuzumab, HR not reported; p not reported.

Table 8. Overall survival (metastatic breast cancer)

Trial	Results
Slamon	Median 25.1 months trastuzumab; 20.37 months no trastuzumab HR not reported, p = 0.046. Relative risk of death .80 (95% CI 0.64−1.00)
M77001	Median 31.2 months trastuzumab; 22.7 months no trastuzumab HR not reported, p (overall survival) = 0.0325

Table 9: Time to treatment failure (metastatic breast cancer)

Trial	Results
M77001	Median 9.8 months trastuzumab; 5.3 months no trastuzumab; HR not reported; p = 0.0001
Slamon	Median 6.9 months trastuzumab; 4.5 months no trastuzumab; HR not reported; p <0.001. Relative risk of treatment failure 0.58 (95% CI 0.47−0.70)

Table 10: Duration of response (metastatic breast cancer)

Trial	Results
M77001	Median 11.7 months trastuzumab; 5.7 months no trastuzumab; HR not reported; p = 0.009
Slamon	Median 9.1 months trastuzumab; 6.1 months no trastuzumab; HR not reported; p <0.001

Table 11: Overall Response (metastatic breast cancer)

Trial	Trastuzumab		No Trastuzumab		Results
	Response rate	Number randomised (Number assessable)	n	Number randomised (Number assessable)	
M77001	61%	94 (92)	34%	94 (94)	p=0.0002
Slamon	50%	235 (235)	32%	234 (234)	p<0.001
Gasparini	73.7%	Not reported (38 evaluable for response)	70.8%	Not reported (24 evaluable for response)	Not reported

TOXICITY AND LONGER TERM SIDE EFFECTS

TREATMENT-RELATED TOXICITY (SHORT-TERM SIDE EFFECTS)

The randomised trials included in this review provided varying amounts of information on the short-term side effects of trastuzumab.

- Slamon classified adverse events as mild, moderate or severe. Abnormalities in laboratory values were classified using the World Health Organisation (WHO) grading system, and cardiac dysfunction using the New York Heart Association (NYHA) grading system. The method used to assign an adverse event to mild, moderate or severe was not reported.
- M77001 classified adverse events using the National Cancer Institute (NCI) Common Toxicity Criteria.
- HERA, NSABPB31 and NCCTG-N9831 reported on the number of adverse events, but did not provide details according to the type of event.
- FinHer did not report the system used to classify adverse events but appears to report using the NCI Common Toxicity Criteria.

It should be noted that most trials did not perform tests for statistical significance in relation to adverse events. Safety is usually assessed based on treatment received and not on treatment allocated. Patients who do not receive treatment are usually excluded from the trials in this review. The adverse events experienced in the randomised trials of trastuzumab are summarised in Table 11 (any or less severe) and Table 12 (severe adverse events).

The Slamon trial reported that patients receiving trastuzumab experienced higher rates of infection (47% v 29%), leukopenia (41% v 26%) and anaemia (27% v 19%). In the trastuzumab arm 25 patients stopped treatment due to adverse events.

The M77001 trial reported a higher overall incidence of grade 3 (67% v 55%) and 4 (34% vs 23%) adverse events in patients receiving the treatment arm containing trastuzumab, although fewer patients in that arm discontinued treatment due to adverse events. The trastuzumab-containing arm also had a higher incidence of grade 3 and 4 leukopenia and neutropenia, and grade 1 and 2 anaemia. Seventeen per cent of patients (15/86) in the trastuzumab-containing arm had an asymptomatic decline in left ventricular ejection fraction (LVEF) of ≥15% (vs 8% in the comparison arm); of these 15 patients, 12 had received prior anthracycline therapy. Two patients had coronary heart failure (CHF); both were in the trastuzumab-containing arm and both had received prior anthracycline therapy.

The HERA trial reported that 7.9% of patients receiving 1 year of trastuzumab had at least one grade 3 or 4 event (7% with at least one serious adverse event, and 0.4% (6 patients) suffering a fatal adverse event) compared to 4.4% of patients in the observation arm (4.7 with at least one serious adverse event, and 0.2% (3 patients) suffering a fatal adverse event).

The joint analysis of NSABPB31 and NCCTG-N9831 reported that '*there was little imbalance between the treatment groups in the incidence of any Common Toxicity Criteria*' except for left ventricular dysfunction (see *Cardiotoxicity* for more details). In the trastuzumab arm of NSABP-B31 there were four cases of interstitial pneumonitis (including one death), and five cases of grade 3+ pneumonitis or pulmonary infiltrates (including one death) in NCCTG-N9831.

The FinHer trial found no significant difference in the frequency of adverse events when trastuzumab was added to docetaxel or vinorelbine.

Table 12: Any or less severe adverse events in randomised trials of trastuzumab

TRIAL (comparison) Severity of event	M77001 any adverse events		FinHer (Docetaxel +/- Trastuzumab) Grade 1 or 2		FinHer (Vinorelbine +/- Trastuzumab) Grade 1 or 2		Slamon adverse events in more than 10% of patients as a group	
Type of adverse event	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab
Abdominal pain	NR	NR	NR	NR	NR	NR	27%	20%
Allergic reaction	NR	NR	13.5%	11.7%	10.0%	2.9%	NR	NR
Alopecia	73%	57%	100.0%	98.0%	50.8%	52.6%	57%	58%
Anemia	NR	NR	63.0%	66.0%	73.8%	66.7%	27%	19%
Anorexia	24%	14%	NR	NR	NR	NR	28%	22%
Arthralgia	29%	21%	NR	NR	NR	NR	20%	14%
Asthenia	49%	44%	NR	NR	NR	NR	57%	56%
Back pain	NR	NR	NR	NR	NR	NR	31%	22%
Chest pain	NR	NR	NR	NR	NR	NR	24%	24%
Chills	NR	NR	NR	NR	NR	NR	38%	8%
Constipation	29%	24%	NR	NR	NR	NR	32%	28%
Increased coughing	NR	NR	NR	NR	NR	NR	43%	26%
Diarrhoea	47%	38%	NR	NR	NR	NR	45%	27%
Dyspnoea not related to heart failure		NR	NR	NR	NR	NR	36%	25%
Elevated aspartate aminotransferase	NR	NR	31.4%	19.2%	58.3%	47.2%	NR	NR
Epistaxis	22%	5%	NR	NR	NR	NR	NR	NR
Erythema	25%	12%	NR	NR	NR	NR	NR	NR
Fatigue	26%	22%	76.0%	83.0%	80.3%	81.4%	NR	NR
Febrile neutropenia / neutropenic sepsis	NR	NR	NR	NR	NR	NR	NR	NR
Fever	NR	NR	NR	NR	NR	NR	53%	29%
Headache	23%	19%	NR	NR	NR	NR	NR	NR
Increased lacrimation	23%	11%	NR	NR	NR	NR	NR	NR
Infection	NR	NR	NR	NR	NR	NR	47%	29%
Infection (no neutropenia)	NR	NR	43.1%	39.2%	32.8%	30.0%	NR	NR
Leukopenia	NR	NR	NR	NR	NR	NR	41%	26%
Mucosal inflammation	25%	23%	NR	NR	NR	NR	NR	NR
Myalgia	29%	28%	NR	NR	NR	NR	23%	22%
Nail problems	NR	NR	47.9%	55.9%	16.4%	9.3%	NR	NR
Nausea	49%	44%	NR	NR	NR	NR	66%	66%
Neuropathy - motor	NR	NR	27.5%	30.5%	13.1%	17.7%	NR	NR
Neuropathy - sensory	NR	NR	57.4%	49.5%	36.1%	43.7%	NR	NR
Neutropenia	NR	NR	0.0%	1.6%	37.7%	28.6%	NR	NR
Neutropenic fever	NR	NR	0.0%	0.0%	0.0%	0.0%	NR	NR
Pain	NR	NR	NR	NR	NR	NR	58%	50%
Parasthesia	35%	22%	NR	NR	NR	NR	29%	23%
(Peripheral) oedema	43%	37%	62.0%	61.6%	37.0%	30.0%	NR	NR
Pharyngitis	NR	NR	NR	NR	NR	NR	27%	16%
Phlebitis	NR	NR	6.0%	8.9%	50.0%	31.1%	NR	NR
Pyrexia	33%	16%	NR	NR	NR	NR	NR	NR
Rash/skin reaction	26%	13%	60.0%	55.6%	18.0%	21.4%	31%	17%
Stomatitis	NR	NR	66.0%	71.1%	50.0%	40.0%	22%	21%
Thrombocytopenia	NR	NR	0.0%	3.7%	0.0%	0.7%	NR	NR
Vomiting	32%	23%	11.8%	10.2%	3.3%	8.6%	47%	40%

Table 13: Severe adverse events in randomised trials of trastuzumab

TRIAL (comparison) Severity of event	M77001 Grade 3 or 4		FinHer (Docetaxel +/- Trastuzumab) Grade 3 or 4		FinHer (Vinorelbine +/- Trastuzumab) Grade 3 or 4		Slamon Severe event	
Type of adverse event	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab	Trastuzumab	No Trastuzumab
Abdominal pain	NR	NR	NR	NR	NR	NR	3%	3%
Allergic reaction	NR	NR	5.8%	2.0%	0.0%	0.0%	NR	NR
Alopecia	11%	6%	not applicable	not applicable	not applicable	not applicable	26%	35%
Anemia	1%	1%	0.0%	0.5%	0.0%	0.2%	2%	2%
Anorexia	2%	0%	NR	NR	NR	NR	<1%	2%
Arthralgia	4%	0%	NR	NR	NR	NR	4%	2%
Asthenia	11%	6%	NR	NR	NR	NR	7%	7%
Back pain	NR	NR	NR	NR	NR	NR	4%	4%
Chest pain	NR	NR	NR	NR	NR	NR	3%	4%
Chills	NR	NR	NR	NR	NR	NR	<1%	<1%
Constipation	2%	0%	NR	NR	NR	NR	1%	3%
Increased coughing	NR	NR	NR	NR	NR	NR	<1%	<1%
Diarrhoea	5%	2%	NR	NR	NR	NR	1%	3%
Dyspnoea not related to heart failure	NR	NR	NR	NR	NR	NR	3%	3%
Elevated aspartate aminotransferase	NR	NR	0.0%	0.2%	3.3%	0.7%	NR	NR
Epistaxis	0%	0%	NR	NR	NR	NR	NR	NR
Erythema	1%	0%	NR	NR	NR	NR	NR	NR
Fatigue	3%	3%	8.0%	8.2%	4.9%	3.2%	NR	NR
Febrile neutropenia / neutropenic sepsis	25%	18%	NR	NR	NR	NR	NR	NR
Fever	NR	NR	NR	NR	NR	NR	8%	4%
Headache	5%	1%	NR	NR	NR	NR	NR	NR
Increased lacrimation	1%	0%	NR	NR	NR	NR	NR	NR
Infection	NR	NR	NR	NR	NR	NR	2%	2%
Infection (no neutropenia)	NR	NR	5.9%	5.0%	1.6%	2.0%	NR	NR
Leukopenia	22%	16%	NR	NR	NR	NR	11%	9%
Mucosal inflammation	2%	4%	NR	NR	NR	NR	NR	NR
Myalgia	3%	3%	NR	NR	NR	NR	3%	3%
Nail problems	NR	NR	not applicable	not applicable	not applicable	not applicable	NR	NR
Nausea	0%	1%	NR	NR	NR	NR	5%	7%
Neuropathy - motor	NR	NR	0.0%	1.4%	1.6%	2.0%	NR	NR
Neuropathy - sensory	NR	NR	0.0%	0.2%	0.0%	1.1%	NR	NR
Neutropenia	35%	23%	100.0%	98.5%	55.7%	58.3%	NR	NR
Neutropenic fever	NR	NR	29.6%	23.0%	4.9%	2.9%	NR	NR
Pain	NR	NR	NR	NR	NR	NR	6%	7%
Parasthesia	0%	2%	NR	NR	NR	NR	<1%	<1%
(Peripheral) oedema	1%	2%	0.0%	1.6%	0.0%	0.0%	NR	NR
Pharyngitis	NR	NR	NR	NR	NR	NR	0%	<1%
Phlebitis	NR	NR	0.0%	0.0%	0.0%	0.0%	NR	NR
Pyrexia	1%	1%	NR	NR	NR	NR	NR	NR
Rash/skin reaction	1%	0%	0.0%	0.0%	0.0%	0.7%	<1%	<1%
Stomatitis	NR	NR	4.0%	2.7%	0.0%	0.0%	<1%	0%
Thrombocytopenia	0%	0%	0.0%	0.0%	0.0%	0.0%	NR	NR
Vomiting	3%	2%	0.0%	0.5%	0.0%	0.5%	5%	7%

CARDIOTOXICITY

Two trials in metastatic breast cancer (Slamon, M77001) and five in early breast cancer (FINHER, HERA, NSABP-B31, NCCTG-N9831, and BUZDAR) have reported data related to cardiac dysfunction (CD) (see Appendix 4). These trials usually pre-specified a range for LVEF as an eligibility criterion for entry into the trial – usually in the range of 45−55%.

Decline in LVEF was the primary indicator of cardiac dysfunction in trial participants and was assessed using a variety of methods including echocardiography and isotope cardiography (multigated acquisition (MUGA) scan). The degree of dysfunction was usually classified using the NYHA classification (eg NSABP-B31) or the NCI Common Toxicity Criteria (eg NCCTG-N9831). Some trials utilised an independent review panel to assess all symptoms related to cardiac function. HERA and NSABP-B31 conducted a cardiac safety analysis relating to stages of accrual with pre-specified incidence of cardiac dysfunction being used as criteria to cease or alter the trial.

Slamon *et al.* were the first to become aware of the potential problem of cardiotoxicity owing to the number of adverse cardiac events reported in that trial. An independent committee retrospectively reviewed all cases of cardiac dysfunction and found an increased incidence of cardiac dysfunction of NYHA class III or IV in patients who had received anthracycline, cyclophosphamide and trastuzumab. In a secondary paper, the investigators further explored cardiac toxicity and found that trastuzumab significantly improved: i) time to progression or any CD; ii) time to progression or NYHA class III or IV cardiac dysfunction; or iii) time to progression or NYHA class III or IV cardiac dysfunction that did not respond to cardiac treatment. There was no detectable difference in cardiac disfunction-free survival. Most patients with cardiac dysfunction in this trial appeared to improve with cardiac treatment.

The M77001 trial reported an overall absolute decrease in LVEF of ≥ 15% in 17% of patients in the trastuzumab arm, and 8% of patients not receiving trastuzumab. Two patients receiving trastuzumab experienced CHF and both had received prior adjuvant anthracyclines to a cumulative dose of 300mg/m^2.[18]

The HERA trial reported a significantly higher incidence of cardiac dysfunction in the group receiving trastuzumab with 29 cases (1.73%) of symptomatic CHF (9 severe) than the observation group (1 case, none severe).

A separate manuscript specifically addressing cardiotoxicity has been published by the NSABP-B31 investigators.[24] The reported analysis was based on all patients accrued to 15 Feb 2005 with cardiac follow-up by 21 April 2005, who had met protocol conditions for initiating trastuzumab. There were cardiac events in 31 of the 815 evaluable patients in the trastuzumab group (all congestive heart failure, no deaths), three of which occurred more than 1 year after initiation of trastuzumab. Twenty seven of these patients had been followed for ≥ 6 months and 26 had been without symptoms of cardiac disease for at least 6 months (18 continued to receive cardiac medications). There were cardiac events in five patients in the group not receiving trastuzumab (four CHF and one probable cardiac death). The relative risk of a cardiac event 3 years after day 1 of cycle 5 was 5.9 in patients receiving trastuzumab compared to those receiving no trastuzumab (95% CI 2.3−15.3, p<0.0001). A

multivariate analysis of risk factors suggested that age and post-AC LVEF were associated with subsequent CHF. The authors reported that CHF associated with trastuzumab responded to “cessation of therapy and management, and LVEF generally recovered to nearly normal levels over time”, although they acknowledged the need for longer follow-up to be able to obtain more information on longer-term toxicity.

In the NCCTG-N9831 trial the 3-year cumulative incidence of CHF (NYHA III/IV) or death from cardiac causes was 2.9% in the trastuzumab group and 0% in the no trastuzumab group.[13] A separate manuscript on cardiac toxicity has also been published by the investigators of this trial however the information published to date pertains only to patients who had received 4 cycles of doxorubicin and cyclophosphamide.[25] It is anticipated that the impact of subsequent trastuzumab will be reported at a future date.

In the FINHER trial, LVEF of the group assigned to trastuzumab was assessed by either echocardiography or isotope cardiography before chemotherapy, after the last FEC cycle, and 12 and 36 months after chemotherapy. It is not reported how patients **not** receiving trastuzumab were monitored for cardiac toxicity other than the routine monitoring for adverse effects (recorded on day 21 of each chemotherapy cycle and 12 and 36 months after chemotherapy – details (including the tests performed) were not reported). There would therefore appear to be differential follow-up based on the allocated intervention. As a result, although the authors conclude that LVEF is preserved in women receiving trastuzumab, it is not possible to evaluate the impact of trastuzumab on cardiac function based on information reported in the publication available for this trial.

LONGER TERM SIDE EFFECTS

The follow-up periods reported in the randomised trials were insufficient for information on longer term side effects to be ascertained. In an attempt to obtain information on longer term side effects, earlier phase (non-randomised) trials were identified. These are described in Appendix 4.

The non-randomised trials do not provide any additional information on longer-term side effects.

TRASTUZUMAB: PREGNANCY AND FERTILITY

A diagnosis of breast cancer may occur during pregnancy or in the 12 months postpartum (including lactation), known as gestational breast cancer (GBC) or pregnancy-associated breast cancer (PABC).[26] It has been estimated that PABC accounts for 0.2−3.8% of all breast carcinomas.[27] From historical case series the median maternal age at the time of diagnosis of breast cancer during pregnancy is estimated at 33−34 years with a gestational age of 17−25 weeks. The reported oestrogen receptor (ER) status of PABC varies with rates between 54% and 80% being reported as ER negative, and 28−58% of cases reported as HER2 positive.[28, 29]

Conventionally it was thought that PABC cases had a poorer prognosis, but newer evidence suggests that it is similar to that of non-pregnant patients of the same age and with the same

stage of disease. Poorer outcomes in this group are more likely related to stage at diagnosis as up to 89% of women presenting while pregnant are lymph node positive.[28–30]

In 2005, Loibl *et al.* published guidelines on how to diagnose and treat women with PABC. These guidelines were the result of a consensus meeting held in September 2003. The methods used to perform the review were not reported (other than a PubMed search using the terms 'breast carcinoma' and 'pregnancy'). The authors of relevant published articles, and other specialists, were invited to participate in the guideline process. The guidelines produced as a result were based on the data presented by participants (including their own data and other summaries of the literature). The authors summarise '*the majority of studies that have examined the pathologic characteristics of PABC and cancer diagnosed during pregnancy*' and conclude that the tumours of pregnant women with breast cancer are similar to those of nonpregnant women in their histopathology and immunohistochemistry (see Table 13).

Table 14: HER2 status in pregnant women

Author	Study design	No. subjects	Her-2 status
Elledge *et al.*	Case control	15 cases (pregnant); 411 controls	HER2+: 58% of cases vs 16% of controls
Shousha *et al.*	Case control	14 cases PABC; 308 controls	HER2+: 44% PABC vs 19% controls
Middleton *et al.*	Prospective case series	38 cases (pregnant amd 1 PABC	HER2+: 28%
Reed *et al.*	Retrospective case series	122 PABC (20 pregnant)	HER2+: 44%

Note: adapted from Table 1 in reference 28

Ring *et al.* attempted to review the literature regarding the diagnosis, management and prognosis of PABC by reviewing English-language articles identified by a search of PubMed using the keywords 'breast cancer and pregnancy', 'chemotherapy and pregnancy' and 'radiotherapy and pregnancy'.[29] The eligibility criteria and other methods used in the review were not reported, the authors stating simply that '*papers were chosen based on their size and adequacy of design*'. In relation to targeted therapy, they concluded that the use of trastuzumab during pregnancy cannot be recommended due to the placental transfer of trastuzumab observed in animal studies.

Trastuzumab has been assigned a pregnancy risk category of B[1] based on extensive trials in monkeys without apparent harm.[31, 32] These studies did however confirm placental transfer of the drug[32, 33] and transfer of the antibody in the milk.[34]

[1] Category B:
Either animal-reproduction studies have not demonstrated a foetal risk but there are no controlled studies in pregnant women, or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).

STUDIES EXAMINING THE IMPACT OF TRASTUZUMAB IN PREGNANT WOMEN

The search strategy in Table 2 was applied in an attempt to identify studies that had investigated the impact of trastuzumab in pregnant women. As a result of this search, three case studies where trastuzumab was received by women during pregnancy were identified (see Table 14). While they may be of interest to readers, and have been summarised in this review, they should not be used as evidence when considering the efficacy or safety of trastuzumab for breast cancer.

One case each was reported in a woman with locally advanced and early breast cancer. In both cases, pregnancy was identified while the women were taking trastuzumab as adjuvant therapy.[32, 35] Anhydramnios (the absence of amniotic fluid) was evident when the pregnancy was discovered at 20 weeks gestation in the case presented by Watson. In this instance, the amniotic fluid index slowly returned to normal after withdrawal of the drug and the birth was induced at 37 weeks. There were no other abnormalities noted. In the second case reported by Waterson *et al.*, the pregnancy was identified very early (in the third or fourth week of pregnancy) and trastuzumab was ceased. This pregnancy followed a normal course and resulted in a normal delivery with no sequelae.

In the case described by Fanale *et al.*, the woman was 27 weeks pregnant when she presented with liver metastases secondary to breast cancer.[34] Treatment consisting of vinorelbine and trastuzumab continued until the birth was inducted at 34 weeks. During this time Oligohydramnios (reduced amniotic fluid) was noted and despite treatment with intravenous fluids, the amniotic fluid index remained low. In addition the birth was induced owing to decreased foetal movement and mild occasional cardiac decelerations. The outcome of this case was a normal uncomplicated delivery.

Table 15: Case studies of trastuzumab in pregnancy

Author and year	Stage of disease	Patient characteristics	Treatment	Outcome
Watson 2005 (35)	Infiltrating ductal carcinoma (T2N3M0) (locally advanced) ER and PR neg	28 yr old woman Pregnancy identified 5 months into course of trastuzumab	Bi-lateral mastectomy plus 4 cycles cyclophosphamide and doxorubicin followed by 4 cycles paclitaxel 6 months following surgery, 8-week course of radiation therapy (60.4 Gy to the chest wall) Subsequently given trastuzumab therapy 6 mg/kg or 580 mg every 3 weeks; last dose of trastuzumab at 20 weeks	Anhydramnios evident at 20 weeks; slowly resolved after the drug was discontinued Labour induced at 37 weeks, vaginal delivery of a female weighing 2,960 grams. Amniotic fluid was clear, placental pathology unremarkable No evidence of abnormal cardiac function
Waterston *et al.* 2006 (32)	Multifocal grade 2 invasive adenocarcinoma with extensive DCIS with 2 of 5 lymph nodes positive (early) ER and PR neg	30 yr old woman Pregnancy identified just prior to 3rd cycle of trastuzumab – conception identified as 3 days following 2nd cycle of trastuzumab.	Bi-lateral mastectomy plus 4 cycles epirubicin 100 mg/m^2 followed by 4 cycles of cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600mg/m^2 (TACT) Radiation therapy (46 Gy in 20 fractions to the chest wall and nodal area) Trastuzumab 736 mg as a loading dose and 523 mg 3 weeks later (HERA)	Discontinued Trastuzumab with intensive monitoring Full term, spontaneous vaginal delivery of a female with no sequelae
Fanale *et al.* 2005 (34)	11B (T2N1MO) initial diagnosis with multiple hepatic metastases 14 months later (stage IV)	26 yr old woman Presented at 27 weeks pregnant, 14 months after her initial treatment with right upper quadrant pain	Trastuzumab loading dose 4 mg/kg and weekly doses of 2 mg/kg Vinorelbine initiated at 25 mg/m^2 weekly for 3 weeks followed by a week of rest	Oligohydramnios noted and treated with IV fluids given with each treatment but amniotic fluid indexes remained low At 34 weeks and 5 days decreased foetal movement was noted with mild occasional cardiac decelerations Labour induced and a vaginal delivery of a health male weighing 5 pounds; no complications noted

WEEKLY VERSUS 3-WEEKLY DOSING SCHEDULES

There are currently no comparative data in either the metastatic or the adjuvant setting directly comparing weekly with 3-weekly schedules of trastuzumab. In a review published in 2002 it was documented that the most commonly used schedule at the time was a loading dose of 4mg/kg given as a 90-minute infusion followed by a weekly maintenance dose of 2mg/kg given over 30 minutes.[36] This is reflected in the schedules used in most of the trials completed to date (see Table 15). The Cancer Care Ontario Program Practice Guideline (2005) addressed the question of optimal dose, schedule and duration of therapy for trastuzumab for metastatic breast cancer and recommends that the weekly schedule should be initiated and maintained until progression or unacceptable toxicity, and suggests that the three-weekly schedule of 6mg/kg may be appropriate for women who prefer the 3-weekly treatment schedule.[37] This guideline also recommends that a switch to the latter schedule may be appropriate following a reasonable period of weekly therapy.

Table 16: Summary of trastuzumab sequence, dose and schedule

Trial	Sequence	Loading dose	Subsequent dose	Dose frequency	Duration of treatment
Early breast cancer					
FinHer	Concurrent	4 mg/kg	2 mg/kg	weekly	9 weeks
HERA	Sequential	8 mg/kg	6 mg/kg	3 weekly	1 v 2 years
NSABPB31	After 4 cycles of AC then concurrently with paclitaxel	4 mg/kg	2 mg/kg	weekly	1 year
NCCTG-N9831	After 4 cycles of AC then concurrently with paclitaxel, or sequentially following paclitaxel	4 mg/kg	2 mg/kg	weekly	1 year
Buzdar	Concurrent (neoadjuvant)	4 mg/kg	2 mg/kg	weekly	24 weeks
BCIRG 006	Concurrent	Not reported	Not reported	Weekly	1 year
Metastatic breast cancer					
Slamon	Concurrent	4 mg/kg	2 mg/kg	weekly	Until progression
M77001	Concurrent	4 mg/kg	2 mg/kg	weekly	Until progression

The pharmacokinetics and safety of the combination of trastuzumab and paclitaxel administered three weekly were investigated in a phase II trial in women with metastatic disease.[38,39] The motivation for the trial was that a 3-weekly schedule (8mg/kg loading dose followed by a 6mg/kg dose) would result in similar exposure to the weekly regimen, would be well tolerated and more convenient. The trial demonstrated that the pharmacokinetics of the weekly and 3-weekly regimens were similar, and estimated that the half life of trastuzumab was 18−27 days. In this study the pharmacokinetics of paclitaxel was not altered. The treatment was well-tolerated and there were no unexpected toxicities. A later phase II study of trastuzumab monotherapy given on a 3-weekly schedule for metastatic disease reported that mean trough trastuzumab concentrations were lower and peak levels were higher

compared with weekly regimens but the 3-weekly regimen did not appear to compromise efficacy or safety.[40]

DISCUSSION AND CONCLUSION

Despite the relative immaturity of many of the studies included in this review, there is sufficient evidence to conclude that trastuzumab is associated with improvements in disease-free survival (and potentially overall survival) in early breast cancer, and progression-free and overall survival in metastatic breast cancer. Trastuzumab was associated with higher rates of infection, leukopenia, anaemia and cardiac dysfunction, and patients experiencing the latter appear to respond to cessation of trastuzumab and appropriate cardiac treatment.

The optimal dose and schedule of trastuzumab remains unknown. Although 3-weekly regimens have become increasingly common they have not been compared directly in randomised trials. Also unanswered is the question of optimal sequence: that is, whether trastuzumab should be administered concurrently or sequentially with chemotherapy, as well as the optimal chemotherapy regimen with which trastuzumab should be combined. There are data from phase II trials examining the use of trastuzumab in combination with other single-agent systemic therapies that have shown evidence of safety and efficacy. Specifically vinorelbine[41–44] and gemcitabine.[45] Data from a phase II trial examining the use of trastuzumab in combination with Celecoxib[46] was unable to show evidence of efficacy. There are a large number of ongoing phase II trials examining the safety and efficacy of using trastuzumab with other single agent systemic therapies, including gefitinib[47] and pertuzumab.[48]

It is unclear whether central nervous system metastases are associated with the biology of HER2-positive breast cancer or develop as a result of trastuzumab treatment. In one trial,[52] 10% of women with metastatic breast cancer receiving trastuzumab in combination with chemotherapy developed isolated central nervous system metastases as first site of tumour progression.

The issue as to whether trastuzumab should be continued following progression requires further investigation. Tripathy *et al*. evaluated the safety of continued trastuzumab use in 93 patients who progressed while on the Slamon trial, with 71 (76%) of these patients receiving chemotherapy plus trastuzumab on progression, and 22 (24%) receiving trastuzumab alone.[49] The authors concluded that trastuzumab was well tolerated, with no new specific adverse events seen with prolonged administration, and no cumulative toxicities. There are at least three ongoing randomised trials investigating treatment in patients who progress on trastuzumab. The SWOG trial S0347 is investigating vinorelbine with or without trastuzumab in patients with metastatic breast cancer who progress during or after taxane therapy in combination with trastuzumab. This trial closed to accrual in January 2006. The BIG3-05 trial is currently recruiting patients who progress during or after chemotherapy plus trastuzumab to a trial comparing capecitabine with or without trastuzumab. The third trial is EGF104900 which is comparing lapatinib with or without trastuzumab in patients who progress while on a trastuzumab-containing regimen.

APPENDICES

APPENDIX 1: DATABASES AND WEB SITES SEARCHED

Organisation	Database/website
NHS Centre for reviews and Dissemination databases/ International Network of Agencies for Health Technology Assessment (INAHTA) Economic evaluation database (EED) Database of abstracts of reviews of effectiveness (DARE) Heath Technology Assessment (HTA)	www.york.ac.uk/inst/crd/
Cochrane Database of Systematic Reviews and Cochrane Controlled Trials Register	www.cochrane.org
British Columbia Office of Health Technology Assessment (Canada)	www.chspr.ubc.ca
Swedish Council on Technology Assessment in Healthcare (Sweden)	www.sbu.se
Oregon Health Resources Commission (US)	http://egov.oregon.gov/DAS/OHPPR/HRC/about_us.shtml
Agency for Healthcare Research and Quality - US Department of Health and Human Services	www.ahrq.gov/clinic/techix.htm
Minnesota Department of Health (US)	www.health.state.mn.us/htac/index.htm
Blue Cross Blue Shield Association – Technology Evaluation Center (US)	www.bcbs.com/tec/index.html
Canadian Coordinating Office for Health Technology Assessment (Canada)	www.ccohta.ca
Alberta Heritage Foundation for Medical Research (Canada)	www.ahfmr.ca
Veteran's Affairs Research and Development Technology Assessment Program (US)	www.va.gov/resdev
National Library of Medicine Health Service/Technology Assessment text (US)	www.hstat.nlm.nih.gov
Office of Health Technology Assessment Archive (US)	www.wws.princeton.edu/~ota
Institute for Clinical Evaluative Science (Canada)	www.ices.on.ca/webpage.cfm
Agence d'evaluation des technologies et des modes d'intervention en sante (Quebec, Canada)	www.aetmis.gouv.qc.ca/site/index.php?accueil
DIMDI - Institute for Medical Documentation and Information (Germany)	www.dimdi.de
National Information Centre of Health Services Research and Health Care Technology (US)	www.nlm.nih.gov/hsrph.html
Health Services/Technology Assessment Text (HSTAT) – National Library of Medicine (US)	www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=hstat
Finnish Office for Health Technology Assessment (FinOHTA) (Finland)	www.stakes.fi/finohta/linkit/
Institute for Medical Technology Assessment (Netherlands)	www.imta.nl/
Danish Centre for Evaluation and Health Technology Assessment (DACEHTA)	www.sst.dk/Planlaegning_og_behandling/Medicinsk_teknologivurdering.aspx?lang=en
Andalusian Agency for Health Technology Assessment (Spain)	www.juntadeandalucia.es/salud/orgdep/AETSA/default.asp?V=EN
Agence Nationale d'Accreditation et d'Evaluation en Sante (France)	www.anaes.fr
NHS Quality Improvement Scotland	www.nhshealthquality.org/
National Coordinating Centre for HTA (NCCHTA) (UK)	www.hta.nhsweb.nhs.uk
The European Information Network on New and Changing Health Technologies	www.euroscan.bham.ac.uk/
Saskatchewan Health Quality Council (Canada)	www.hqc.sk.ca
Institute for Clinical Systems Improvement (ICSI)	www.icsi.org
Centre for Health Economics (Australia)	www.buseco.monash.edu.au/centres/che/

APPENDIX 2: CHARACTERISTICS OF INCLUDED STUDIES

Table 16. Characteristics of included trials in early breast cancer

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
FINHER (10)	Accrual: 10/2000 to 09/2003 Multicentre, national Number of patients recruited: 1010 (232 HER2+)	Female Age: eligible if <66 Median age recruited 50.8 (25.5−65.7) in docetaxel arm, 51.0 (26.9−65.8) in vinorelbine arm Stage: early breast cancer. Eligible patients had at least 1 positive axillary node, or node negative breast cancer mass of at least 20 mm in diameter. PR negative Both HER2 positive and negative included. No specific reference to inflammatory disease. HER2 status ascertained by IHC, according to guidelines at each institution. Normal cardiac function.	HER2 negative randomised to one of: ARM 1: docetaxel 100 mg/m^2 + FEC ARM 2: Vinorelbine 25 mg/m^2 + FEC HER2 positive randomised to one of: ARM 3: docetaxel 100 mg/m^2 + FEC, no trastuzumab ARM 4: docetaxel 100 mg/m^2 + FEC + trastuzumab (loading dose 4 mg/kg then 2 mg/kg weekly) ARM 5: Vinorelbine 25 mg/m^2 + FEC, no trastuzumab ARM 6: Vinorelbine 25 mg/m^2 + FEC + trastuzumab (loading dose 4 mg/kg then 2 mg/kg weekly) 21-day cycles. Docetaxel given day 1; vinorelbine days 1, 8 and 15, trastuzumab weekly (for 9 infusions). FEC commenced after completion of docetaxel / vinorelbine treatment = fluorouracil 600 mg/m^2 day 1; epirubicin 60 mg/m^2 day 1; cyclophosphamide 600 mg/m^2 day 13 x 21 day cycles	**Primary**: • Recurrence-free survival (time from date of randomisation to date of detection of local, distant or contralateral invasive breast cancer, or death). **Secondary** • Adverse effects • LVEF • Time to distant recurrence • Overall survival (time from randomisation to death from any cause) Note: 1 woman excluded from survival analysis in trastuzumab arm with overt metastases at study entry	Median follow-up 36 mo (20−55 mo) Note: the trial was designed to address the question of docetaxel + FEC v vinorelbine + FEC Trastuzumab appears to be a secondary question.	Sequence generation to docetaxel or vinorelbine was by permuted blocks, stratified by HER2 status. Allocation concealment: centralised randomisation (details not described) HER2 positive women were randomly assigned to receive or not to receive trastuzumab. Sequence generation and allocation concealment not described

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
HERA (11) Updated in (12)	Accrual: 12/2001 to 03/2005 Multicentre, international Randomisation stratified Number of patients recruited: 5090 (5081 in analysis) • 1694 2 yr trastuzumab • 1694 1 yr trastuzumab • 1693 observation Investigators: Breast International Group (BIG) (Europe)	Female Age: no age restrictions in eligibility criteria; median age recruited 49 Stage: node positive or negative disease if tumour >1cm on pathology; no distant metastases; locally advanced and inflammatory disease excluded LVEF normal (≥55%) Completed at least 4 cycles of adjuvant and/or neoadjuvant chemotherapy HER2 status as assessed in the participating institution	ARM 1: Trastuzumab 8 mg/kg once then 6 mg/kg every 3 wks for 2 yrs ARM 2: Trastuzumab 8 mg/kg once then 6 mg/kg every 3 wks for 1 yr ARM 3: Observation only	**Primary endpoint** • Disease free survival (defined as time from randomisation to the 1st occurrence of: recurrence of breast cancer at any site, ipsilateral or contralateral breast cancer (incl DCIS, excl LCIS), 2nd cancer (not BCC, SCC of skin, CIS cervix), or death from any cause) **Secondary endpoints:** • Overall survival • Cardiac safety • Site of 1st disease-free survival event • Time to distant recurrence (defined as time between randomisation and the date of the 1st distant tumour recurrence)	Median follow-up 1 yr (0−36 mo) Note: the full published article reports interim results for 1 yr trastuzumab vs observation Adverse effects reported by treatment received not treatment allocated The abstract reported at ASCO 2006 reports median follow-up of 2 yrs	Sequence generation: minimisation Allocation concealment: not described
NSABP-B31 (13)	Accrual: 02/2000 to 04/2005 Multicentre, national Number of patients recruited 2043 (reports on 1736 with at least one follow-up evaluation) Investigators: National Surgical Adjuvant Breast and Bowel Project (USA)	Female Age: no age restrictions in eligibility criteria Stage: IIA, IIB or IIIA (T1−3, N0−1, M0); at least 1 axillary node histologically positive. No specific reference to inflammatory disease LVEF ≥ lower limit of normal Must have undergone axillary dissection and either total mastectomy or lumpectomy HER2 strongly positive (IHC 3+ or FISH+).	ARM 1: doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) every 3 wks for 4 cycles, ***followed by*** paclitaxel (175 mg/m^2) every 3 wks for 4 cycles ARM 2: doxorubicin (60 mg/m^2) + cyclophosphamide (600 mg/m^2) every 3 wks for 4 cycles, ***followed by*** paclitaxel (175 mg/m^2) every 3 wks + trastuzumab (loading dose 4 mg/kg for 1st wk, followed by weekly doses of 2 mg/kg) starting the same time as paclitaxel for 52 wks.	**Primary endpoint** • Disease-free survival Defined as local, regional or distant recurrence; contralateral breast cancer (incl DCIS); other 2nd primary cancers; death before recurrence or a 2nd primary cancer; time (start) not defined. **Other endpoints** • Overall survival • Time to distant recurrence • Death from breast cancer • Contralateral breast cancer • Other 2nd primary cancers • Adverse events	Median follow-up 2.4 yrs Note: reports interim results. Data are reported as combined analysis with NCCTG-N9831	Sequence generation: biased coin minimisation Allocation concealment: not reported

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
NCCTG-N9831 (13)	Accrual: 05/ 2000 to 04/2005 Multicentre, national Number of patients recruited: 1633 (reports on 1615 enrolled in Groups A or C with follow-up data) Investigators: North Central Cancer Treatment Group (USA)	Female Age: 18 and over in eligibility criteria in protocol. Stage: Early breast cancer (T1−3, pN1−2, M0); one or more positive lymph nodes. No specific reference to inflammatory disease. LVEF normal Must have undergone complete resection of the primary tumor and axillary dissection (negative sentinel node biopsy allowed) HER2 positive (IHC 3+ or FISH+).	All patients received 4 cycles of AC (doxorubicin 60 mg/m^2 + cyclophosphamide 600 mg/m^2 every 3 wks). Then received randomised treatment: ARM 1: paclitaxel 80 mg/m^2 weekly from week 13 for 12 wks ARM 2: paclitaxel 80 mg/m^2 weekly from wk 13 for 12 weeks then trastuzumab (4 mg/kg loading dose -> 2 mg/kg) weekly from wk 25 for 52 wks ARM 3: paclitaxel 80 mg/m^2 + trastuzumab (4 mg/kg loading dose -> 2 mg/kg) weekly from wk 13 for 12 weeks then trastuzumab (2 mg/kg) weekly for another 40 wks (total 52 wks)	**Primary endpoint** • Disease-free survival. Defined as local, regional or distant recurrence; contralateral breast cancer (incl DCIS); other second primary cancers; death before recurrence or a second primary cancer. Time (start) not defined. **Other endpoints** • Cardiotoxicity • Overall survival • Time to distant recurrence • Death from breast cancer • Contralateral breast cancer • Other second primary cancers • Adverse events	Median follow-up 1.5 yrs	Sequence generation: dynamic allocation Allocation concealment: not reported
BUZDAR (14)	Accrual: 06/2001 to 10/2003 Multicentre, national Randomisation stratified blocks, strata based on age and stage of disease Number of patients recruited: 42 Note: a trial of neoadjuvant chemotherapy Investigators: MD Anderson Cancer Center (USA)	Female Age: median 48 in Arm 1 (range 25−75); median 52 in Arm 2 (range 29−71) Stage: operable breast cancer (stage II to IIIA). Inflammatory disease excluded. Cardiac ejection fraction ≥ 45% HER2 positive (IHC 3+ or FISH+)	ARM 1: 4 cycles paclitaxel (225 mg/m^2) repeated every 3 wks ***followed by*** 4 cycles of fluorouracil, epirubicin, cyclophosphamide (FEC) ARM 2: 4 cycles paclitaxel (22 5mg/m^2) repeated every 3 wks ***followed by*** 4 cycles of fluorouracil, epirubicin, cyclophosphamide (FEC) ***plus*** simultaneous weekly trastuzumab (2 mg/kg) for 24 wks Then local therapy: surgery +/− axillary dissection +/− radiation therapy	**Primary endpoint** • Pathologic complete response (pCR) rate **Other endpoints** • Clinical response • Toxicity	Median follow-up 20 mo (8.8–36.6 mo) Note: this trial closed early based on the results of an unscheduled interim analysis, conducted as a result of surgeons noting the high complete response rate.	Sequence generation: stratified block Allocation concealment: not reported

Table 17. Characteristics of included trials in metastatic breast cancer

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Vogel (21;50) (UCLA-HSPC-9510492; NCI-V96-0947)	Accrual dates: Multicentre, multi national (USA and Canada) Line: first Number of patients recruited: 114	Female Mean age recruited: 54 (range 28−86) Stage: metastatic. No specific reference to inflammatory disease Cardiac function: excluded clinically significant cardiac function HER2 positive (IHC 2+ or 3+)	ARM 1: Trastuzumab (4 mg/kg loading dose then 2 mg/kg) weekly ARM 2: Trastuzumab (8 mg/kg loading dose then 4 mg/kg) weekly	**Primary**: • Response • clinical benefit (CR, PR or SD longer than 6 months) **Secondary** • duration of response • time to disease progression • survival • quality of life	Median follow-up not reported Note: this trial was designed "to explore the activity and tolerability of trastuzumab at 2 dose levels. No formal statistical comparisons were made between the 2 dose groups." Note: most outcomes are not reported by treatment arm	Sequence generation: not reported Allocation concealment: not reported
BCIRG 007 (20) (UCLA-0109024; NCT00047255; nci-g02-2116) Note: reported in abstract form only.	Accrual dates: not reported Multicentre, international Line: first Number of patients recruited: 263 (target 444)	Female Age: eligible if 18−75 Age recruited not reported Stage: stage IIIB, IIIC or IV. No specific reference to inflammatory disease. Cardiac function: LVEF normal HER2 positive: not defined	ARM 1: Trastuzumab (dose unspecified) and docetaxel (100 mg/m^2) ARM 2: Trastuzumab (dose unspecified), docetaxel (75 mg/m^2) and carboplatin (AUC 6) Trastuzumab was given as a loading dose of 4 mg/kg then 2 mg/kg weekly followed by 3 weekly at 6 mg/kg until progression 21-day cycles for up to 8 courses or until disease progression or unacceptable toxicity. After 8 courses, trastuzumab continued every 3 wks	**Primary**: • time to disease progression **Secondary** • response • duration of response • overall survival • clinical benefit (CR, PR or SD for more than 24 wks) • toxicity	Median follow-up: not reported Note: the question addressed in this trial is the addition of carboplatin to trastuzumab.	Sequence generation: not reported Allocation concealment: not reported

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Slamon Note: the primary publication is (16) Separate publications are available for cardiac dysfunction (51) (51), central nervous system metastases (52) and quality of life (53).	Accrual dates: 06/1995 − 03/1997 Multicentre, national Line: first Number of patients recruited: 469	Female Median age recruited: mean 51−4 (range 25−77) Stage: metastatic. No specific reference to inflammatory disease. Cardiac function: not reported HER2 positive (IHC 2+ or 3+)	ARM 1: Chemotherapy alone ARM 2: chemotherapy plus Trastuzumab Chemotherapy = anthracycline (doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2) plus cyclophosphamide, or paclitaxel 175 mg/m^2 if received prior anthracycline. Once every 3 wks for 6 cycles. Trastuzumab weekly (4 mg/kg loading dose then 2 mg/kg) until disease progression)	**Primary**: • time to disease progression • incidence adverse effects **Secondary** • response rate • response duration • time to treatment failure • overall survival	Median follow-up 30 mo (range 30−51)	Sequence generation: not reported Allocation concealment: not reported
CALGB 9840 (19) (CLB 9840; NCT00003440) Note: reported in abstract form only. This trial started randomising HER2 positive and negative patients to Trastuzumab. After the first 171 patients, HER2 positive received Trastuzumab and HER2 negative continued to be randomized.	Accrual dates: not reported Multicentre, national (USA) Line: first (488) or second (97) Number of patients recruited: 585	Female Age: eligible if 18 or over Median age recruited: not reported Stage: metastatic. No specific reference to inflammatory disease. Cardiac function: not reported HER2 positive not defined.	ARM 1: paclitaxel (175 mg/m^2) 3 weekly ARM 2: paclitaxel (80 mg/m^2) weekly ARM 3: paclitaxel (175 mg/m^2) 3 weekly, plus trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly ARM 4: paclitaxel (80 mg/m^2) weekly, plus trastuzumab 4 mg/kg loading dose, then 2 mg/kg weekly 21-day cycles until disease progression or unacceptable toxicity. HER2 positive only randomised to ARM 3 or 4	**Primary**: • response **Secondary** • time to progression • overall survival • quality of life • cardiac toxicity	Median follow-up not reported Protocol states patients followed at 6, 12 and 18 mo, then annually for 5 yrs or until death Note: does not report data on the trastuzumab comparison	Sequence generation: not reported Allocation concealment: not reported

Study ID	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
M77001 (18, 54)	Accrual dates: 04/2000 to 10/2002 Multicentre, multinational Line: first Number of patients recruited: 188	Female Age: eligible if 18−70 Median age recruited: Arm 1 55 (24−79), Arm 2 53 (32−80) Stage: metastatic. No specific reference to inflammatory disease. Cardiac function: LVEF >50% HER2 positive (IHC 2+ or 3+; protocol amendment (unclear when) to IHC 3+ and/or FISH+)	ARM 1: docetaxel (100 g/m^2) every 3 wks for 6 cycles ARM 2: docetaxel (100 g/m^2) every 3 wks for 6 cycles plus trastuzumab (4 mg/kg loading dose then 2 mg/kg) until disease progression	**Primary**: • overall response rate **Secondary** • toxicity • duration of response • time to disease progression • time to treatment failure • overall survival	Median follow-up not reported	Sequence generation: not reported Allocation concealment: not reported
Gasparini (17) Note: reported preliminary results in abstract form only	Accrual dates: not reported Multicentre, national Line: first Number of patients recruited: 82 to April 2003.	Female Age: eligible if ≥18 and ≤70 Median age recruited 53 (30−69) Stage: metastatic. No specific reference to inflammatory disease. Cardiac function: not reported HER2 positive (IHC 2+ or 3+)	ARM 1: paclitaxel (80 g/m^2) weekly ARM : paclitaxel (80 g/m^2) weekly plus trastuzumab (4 mg/kg loading dose then 2 mg/kg)	• toxicity • response	Median follow-up not reported	Sequence generation: not reported Allocation concealment: not reported

APPENDIX 3: CHARACTERISTICS OF ONGOING STUDIES

Table 18. Characteristics of ongoing randomised trials in early and/or locally advanced breast cancer

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
GMA TAX 302 (BCIRG 006) (9)	Design: A multicentre phase III randomised controlled trial with three treatment arms. Patients stratified according to participating centre, nodal status (node negative versus 1−3 positive nodes vs 4 or more positive nodes)	Women aged 18−70 yrs with histologically confirmed operable breast cancer T1−3, NO−1, M0 Lymph node positive disease OR high-risk lymph node negative disease (tumour size >2cm, nuclear grade 2−3, under 35 yrs HER2-neu gene amplification by FISH Hormone receptor status known No previous or known cardiovascular history (CHF, ischaemia, infarction, arrhythmia) No prior immunotherapy, chemotherapy or hormonal therapy for BC	Setting: Adjuvant Comparison of doxorubicin and cyclophosphamide followed by docetaxel (AC-T) with docetaxel, carboplatin and Trastuzumab (TCH) Arm 1 – AC (60/600 mg/m^2 q3wk x4) followed by T (100 mg/m^2 q3wk x4) Arm 2 – AC (60/600 mg/m^2 q3wk x4) followed by T (100 mg/m^2 q1wk during chemo/q3wk during FUP) + H (trastuzumab continuing once weekly for 1 yr from the initial dose) Arm 3 – TC (75 mg/m^2/AUC6 q3wk x 6) + H (trastuzumab continuing once weekly for 1 yr from the initial dose) The dose of trastuzumab used in this trial has not been reported. Follow up: at 1 and 3 mo for 2 yrs, every 6 mo for 3 yrs and annually for 5 yrs	• Disease free survival • Overall survival • Safety including cardiotoxicity	Current status: Closed to accrual Target accrual: From protocol – 3,150 patients (1050 per treatment arm) over 2.5 yrs Starting date: Accrual April 2001−March 2004 Note: Interim analysis conducted and reported on 3222 patients with a medium follow up of 23 mo at ASCO 2006

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
E-2198	Design: Phase II randomised Pilot Study Patients stratified according to radiotherapy (none planned versus planned to breast or chest wall) Follow-up every 3 mo for 1 yr, every 6 mo for 2 yrs, and then annually thereafter	Women aged 18 and over with histologically confirmed stage II or IIIA (T1−3, N1−2, M0) adenocarcinoma of the breast HER2 expression 2+ or 3+ (IHC) Local breast cancer surgery within past 6 wks with clear surgical margins AND axillary lymph node dissection with at least 6 nodes removed No prior chemotherapy, radiotherapy or hormonal therapy for BC No history of cardiomyopathy, no CHF or arrhythmia within last 6 months LVEF at least 50%	Setting: Adjuvant Study of paclitaxel plus trastuzumab (TH) followed by adjuvant doxorubicin plus cyclophosphamide (AC) compared with the same regimen and trastuzumab (H) for 12 mo Arm 1: T(175 mg/m^2 q3w x4) + H (4 mg/m^2 loading dose followed by 2 mg/m^2 x 9w) Followed by AC (over 1 hr every 3 wks for 4 courses). Following chemotherapy, oestrogen receptor (ER) positive and/or progesterone receptor (PR) positive patients receive oral tamoxifien twice daily for 5 yrs. Arm 2: Same as arm 1 – followed by 52 wks of trastuzumab). ER and/or PR positive patients receive tamoxifen as in Arm 1 but may be concurrent with trastuzumab. Follow-up every 3 mo for 1 yr, every 6 mo for 2 yrs, and then annually thereafter	• Safety including cardiotoxicity	Current status: Closed to accrual Target accrual: 110 patients (50 each arm) within 1 yr (from protocol) Note: Interim analysis reported on 234 patients at San Antonio 2001

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
PACS 04 FRE–FNCLCC–04/0005, EU-20236	Design: multicentre phase III randomised open label Patients stratified according to participating centre and treated in two parts	Women aged 18−64 with histologically confirmed nonmetastatic adenocarcinoma of the breast with lymph node invasion (N1, N2 or N3), Assessment of HER2 status not described although only those patients who were HER2 positive moved into part two of the trial Complete surgical resection with clear margins including the removal of at least 5 lymph nodes within the last 42 days At least 4 weeks since prior chemotherapy, no prior hormonal therapy, no prior radiotherapy LVEF at least 50%	Setting: Adjuvant Comparison of 6 cycles of 5-fluorouracil – epirubicin- cyclophosphamide (FEC) with 6 cycles of epirubicin-docetaxel (ET) followed by sequential trastuzumab (H) All patients undergo radiotherapy 5 days/wk for 5 wks following chemotherapy. Patients with hormone (oestrogen or progesterone) receptor-positive tumours also receive oral tamoxifen daily beginning after chemotherapy is completed and continuing for 5 yrs. Trial 1: ARM 1 − FEC 100 (F and C 500 mg/m^2, E 100 mg/m^2 treatment repeats every 3 wks for 6 courses). ARM 2: ET75: (E 75 mg/m^2, T 75 mg/m^2. treatment repeats every 3 wks for 6 courses) Trial 2: Patients with HER2/neu-positive randomised to: Arm 1: Observation only Arm 2: 1 yr of monotherapy with H (6 mg/kg iv every 3 wks)	• Efficacy of two forms of adjuvant chemotherapy on 5 yr survival • Efficacy and tolerability of trastuzumab in patients with hormone receptor-positive tumours • Overall survival • Toxicity • Quality of life	Current status: Closed to accrual Target accrual: From protocol 2600 patients within 3 yrs Starting date: 2003 Note: Interim analysis reported on 3010 patients at ASCO 2006 but this did not report data relating to trastuzumab

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
CLB 49808	Design: Multicentre phase III randomised, open-label controlled trial 2 x 2 x 2 factorial design Patients stratified according to stage (inflammatory versus non inflammatory inoperable stage III/regional stage IV vs operable stage III. Patients randomised to one of 8 treatment arms	Women 18 yrs and over with histologically confirmed infiltrating adenocarcinoma of the breast T3, N1, M0 Any T, N2, or N3, M0 T4, any M, M0 OR Supraclavicular or infraclavicular lymph nodes as the onlt site of metastasis HER-2 amplification by FISH Oestrogen and progesterone receptor positive or negative No prior or concurrent chemotherapy No more than 4 weeks of tamoxifen or longer than 4 weeks if chemoprevention. No other hormonal therapy No prior radiotherapy except contralaterally LVEF normal by MUGA	Setting: Neoadjuvant Doxorubicin and cyclophosphamide (AC) with or without dexrazoxane followed by paclitaxel (T) with or without Trastuzumab (H) Arm 1: Dexrazoxane + AC T+H + Surgery + radiotherapy + H x 40 wks Arm 2: Dexrazoxane + AC T+H + Surgery + radiotherapy + observation x 40 wks Arm 3: Dexrazoxane + AC T + Surgery + radiotherapy + H x 40 wks Arm 4: Dexrazoxane + AC T + Surgery + radiotherapy + observation x 40 wks Arm 5: AC + T+ H + Surgery + Radiotherapy + H x 40 wks Arm 6: AC + T+ H + Surgery + Radiotherapy + Observation x 40 wks Arm 7: AC + T + Surgery + Radiotherapy + H x 40 wks Arm 8: AC + T + Surgery + Radiotherapy + Observation x 40 wks Follow up every 6 mo for 5 yrs and then annually for 5 yrs	• Survival • Recurrence • Disease free survival • Response • Toxicity including cardiotoxicity • Rates of breast conserving treatment	Current status: Completed Target accrual: From protocol 396 patients within 4 yrs Starting date: 2001

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
UCLA 9911084	Design: Multicentre phase II study. Patients stratified according to age, initial tumour size, tumour type (T2 versus T3 versus T4), presence of clinically positive lymph nodes (yes/no) and mother's family history (positive versus negative)	Women aged 18−80 yrs with a histologically or cytologically confirmed infiltrating adenocarcinoma of the breast (tumour greater than 2cm (T2, T3) or skin and chest wall involvement (T4) and N, M0 HER-2 FISH No prior trastuzumab or other immunotherapy No prior docetaxel/carboplatin or concurrent chemotherapy No prior hormonal therapy No prior or concurrent radiotherapy LVEF normal by MUGA or echocardiogram	Setting: Neoadjuvant and adjuvant Neoadjuvant docetaxel and carboplatin (TC) with versus without trastuzumab (H) Neoadjuvant therapy: All patients receive docetaxel IV over 1 hour and carboplatin IV over 30−60 min on day 1 or 2. Treatment repeats every 21 days for up to 4 courses in the absence of disease progression or unacceptable toxicity. Patients who are HER2/neu positive are randomised to 1 of 2 concurrent trastuzumab treatment arms. Arm I: Trastuzumab (concurrently with chemotherapy) IV over 30−90 min on days 1, 8, and 15. Trastuzumab repeats every 21 days for up to 4 courses in the absence of disease progression or unacceptable toxicity. Arm II: Patients do not receive concurrent trastuzumab. Patients receive neoadjuvant chemotherapy only. Surgery: Within 3 wks after completion of course 4 of neoadjuvant therapy, patients with responding disease undergo definitive surgery. Adjuvant therapy: Within 4−6 wks after surgery, patients with responding disease receive 4 additional courses of docetaxel and carboplatin as during neoadjuvant chemotherapy. All HER2/neu positive patients also receive trastuzumab IV once weekly for 12 wks and then every 3 wks for 40 wks (total of 52 wks of trastuzumab therapy). Within 6 wks after adjuvant chemotherapy, patients undergo radiotherapy. Patients are followed annually for 5 yrs.	• Response • Toxicity • Disease free survival • Overall survival	Current status: Currently recruiting Target accrual: From protocol 75 patients within 4 yrs Starting date: 2003

Table 19. Characteristics of ongoing randomised trials in metastatic breast cancer

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
SWS-SAKK-22/99, EU-99028	Design: Multicentre phase III randomised study Patients stratified according to degree of HER2/neu overexpression (2+ vs 3+), prior anthrycycline – containing adjuvant treatment (no prior treatment vs prior treatment without RT to left chest wall vs prior treatment with RT to left chest wall), estrogen receptor status (positive vs negative vs unknown), prior therapy (1st line vs 2nd/3rd) and centre	Women aged 18−70 yrs with histologically confirmed HER2-overexpressing MBC; clinically or radiologically evaluable disease Prior adjuvant or neoadjuvant chemotherapy allowed but no more than 2 prior CT regimens for MBC, no prior cumulative dose of doxorubicin > 240 mg/m^2 or epirubicin > 360 mg/m^2, no prior taxanes Prior adjuvant hormonal therapy for MBC allowed No ascitic, pleural or pericardial effusions, osteoblastic bone or lung metastases, no brain or meningeal involvement. Life expectancy at least 12 wks LVEF normal with no history of cardiac abnormalities	Setting: First line metastatic Trastuzumab alone followed by combination trastuzumab and paclitaxel versus first-line combination trastuzumab and paclitaxel in women with HER2-overexpressing MBC Arm 1: Trastuzumab IV weekly. At disease progression patients receive combination trastuzumab and paclitaxel IV as in arm 2. Arm 2: Trastuzumab iv weekly. Paclitaxel administered IV weekly for 3 wks followed by 1 wk of rest. Treatment continues until toxicity or disease progression. Patients are followed at 1, 3 and 6 mo and every 6 mo thereafter	• Efficacy • Toxicity • Quality of life • Serum HER2/neu ECD levels on clinical outcomes	Current status: Active Target accrual: From protocol 170−250 patients (850125) per arm Starting date: 2000
ROCHE – BO16216 (TAnDAM), CWRU – 030118, GENENTECH – H2223g, ROCHE – 1100, ROCHE – B016216C	Design: Multicentre, Phase II/III open label randomised study Patients stratified according to liver metastases (yes, no), tumour assessment (evaluable vs measurable), relapse after prior adjuvant tamoxifen treatment (no prior adjuvant tamoxifen vs relapse at least 12 mo after therapy vs relapse during or < 12 mo after therapy, and current bisphosphonate therapy (yes vs no)	Postmenopausal women ≥ 60 yrs or < 60 yrs and amenorrheic for at least 12 mo with histo-/cytologically confirmed MBC and HER2 overexpression (3+) or amplification (≥ 2-fold) by FISH Hormone receptor status: oestrogen and/or progesterone receptor positive No evidence of CNS metastases At least 6 mo since prior adjuvant chemotherapy and no prior chemotherapy for MBC Prior first-line tamoxifen for metastatic disease allowed if partial or complete response or stable disease > 6 mo No prior radiotherapy to indicate lesion and no concurrent radiotherapy	Setting: First line metastatic Anastrozole with or without trastuzumab Arm 1: Oral anastrozole once daily and trastuzumab IV weekly Arm 2: Oral anastrozole once daily Treatment continues in both arms for at least 2 yrs in the absence of disease progression or unacceptable toxicity. Patients are followed at 28 days	• Progression-free survival • Safety profile • Overall clinical-benefit rate Overall survival/2 yr survival • Response	Current status: Closed Target accrual: From protocol 202 patients (101) per arm to be accrued within 24 mo Starting date: 2001

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
		LVEF ≥ 50% and no uncontrolled cardiac disease or cardiac abnormalities			
EORTC-10995, EORTC-16999	Design: Multicentre Phase II randomised study Patients stratified according to participating centre, prior regimens for metastatic disease (none vs one), ECOG status (0-1 versus 2), and visceral disease (yes vs no)	Women aged 18 yrs and over with histologically confirmed MBC and 3+ overexpression on HERCEP test No more than 1 prior CT regimen for MBC Prior combination of cyclophosphamide, methotrexate, and fluorouracil (CMF) allowed in adjuvant/metastatic setting only if disease-free interval after completion was at least 12 mo Prior anthracyclines and/or taxanes allowed with 4 wks since anthracycline therapy No prior cumulative dose of doxorubicin > 360 mg/m^2 or epirubicin > 720 mg/m^2 or mitoxantrone > 90 mg/m^2 More than 2 wks since hormonal therapy in the adjuvant or metastatic setting No concurrent RT No CNS metastases LVEF normal by MUGA and no clinical heart failure	Setting: First and second line MBC Cyclophosphamide, methotrexate, and fluorouracil (CMF) with or without trastuzumab Arm 1: CMF every 4 wks for 8 courses. Arm 2: CMF every 4 wks for 8 courses and trastuzumab weekly then trastuzumab alone every 3 wks Treatment continues until disease progression, unacceptable toxicity or patient refusal Patients are followed every 8 wks until disease progression or initiation of a new anticancer therapy. Patients developing disease progression are followed every 12 wks	Incidence of clinical heart failure Objective response Time to progression Toxicity	Current status: Closed 27/2/2006 Target accrual: From protocol 54−132 patients (27−66 per treatment arm) to be accrued within 2 yrs Starting date: 2002

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
SWOG-S0347,	Design: Multicentre phase III randomised study	Women aged 18 yrs and over with histologically confirmed breast cancer and clinical evidence of metastatic disease HER2-positive tumor, indicated as HER2 gene amplification by FISH or 3+ IHC Disease progression during or after taxane therapy in combination with trastuzumab as first or second line CT for MBC At least 28 days since prior trastuzumab Prior adjuvant/neoadjuvant chemotherapy allowed for a total of 3 regimens. No more than 2 prior CT regimens for MBC No other prior chemotherapy after progression on a taxane/trastuzumab regimen No prior cumulative dose of anthracycline based CT > 360 mg/m^2 No prior hormonal therapy after progression on a taxane/trastuzumab regimen No leptomeningeal disease or lymphatic pulmonary metastases. Brain metastases allowed provided disease is stable for > 3 mo after completion of prior RT LVEF ≥ 50% - no significant cardiac disease	Setting: Second or third line MBC Vinorelbine with versus without trastuzumab Arm 1: Trastuzumab and vinorelbine on day 1 of course 1. Trastuzumab and vinorelbine IV on days 1, 8, 15, 22 in all subsequent courses. If Trastuzumab is discontinued, patients continue to receive vinorelbine Arm 2: Vinorelbine IV on days 1, 8, 15 and 22 Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity Patients followed up every 3 mo and then every 6 mo for up to 3 yrs	• Progression-free survival • Overall survival • Time to treatment failure • Toxicity • Response rate	Current status: Closed 2/1/2006 Target accrual: From protocol 292 patients (146 per treatment arm) Starting date: 2003

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
GBG26, BIG3-05	Design: Multicentre, controlled, non blinded, randomised phase III study	Women aged 18 yrs and over with pathologically confirmed locally advanced or metastatic disease not suitable for surgery or radiotherapy alone HER2- overexpression of the primary or metastatic tumour IHC or FISH amplification. HER2 positive primary tumours with HER2 negative metastasis also included Disease progression during or after previous CT and trastuzumab treatment (provide 12 wks of treatment). Treatment free period of trastuzumab 6 wks • Taxanes + trastuzumab as adjuvant therapy • Taxanes + trastuzumab as 1st line palliation • Trastuzumab given as 1st line palliation alone or in combination with chemotherapeutic agents other than capecitabine ot taxanes No more than one CT for palliation At least 4 wks since surgery or RT Life expectancy > 3 mo LVEF ≥ 50% - no significant cardiac disease	Setting: Second line MBC Capecitabine versus capecitabine and trastuzumab Arm 1: Capecitabine 2500 mg/m^2 orally day 1−14q day 22 until progression Arm 2: Capecitabine 2500 mg/m^2 orally day 1−14q day 22 until progression plus trastuzumab 6 mg/kg every 3 weeks IV until progression	• Time to disease progression • Response	Current status: Active Target accrual: Not stated Starting date: Unknown

Study ID	Trial Name	Participants	Interventions	Outcomes	Notes
EGF104900	Design: Phase III	Women aged 18 yrs and over with MBC HER2 amplification FISH and measurable disease Previous treatment with taxane, anthraycycline and trastuzumab containing regimens with documented progression on the trastuzumab containing regimen LVEF within normal range	Setting: metastatic (line not specified) Arm 1: Lapatinib plus trastuzumab Arm 2: Lapatinib monotherapy	• Safety and efficacy	Current status: Active Target accrual; Not stated Starting date: Unknown
EGF104383	Design: Phase III with initial open label safety cohort of 20 patients to assess the tolerability of the triple combination	Women with confirmed advanced Stage IV BC Erb2 overexpressing MBC Adequate cardiac function and free of brain metastasis Progression > 1 yr following treatment with taxanes. More than 1 yr since traztuzumab	Setting: First line metastatic Paclitaxel trastuzumab and lapatinib versus paclitaxel trastuzumab and placebo Arm 1 : Paclitaxel 80 mg/m^2 IV weekly for 3 wks of a 4-wk cycle, trastuzumab 4 mg/kg as loading dose and then 2 mg/kg IV and oral lapatinib 1000 mg QD Arm 2 : Paclitaxel 80 mg/m^2 IV weekly for 3 wks of a 4-wk cycle, Trastuzumab 4 mg/kg as loading dose and then 2 mg/kg IV and placebo	• Time to progression • Overall response • Progression free survival • Overall survival	Current status: Active Target accrual: Not stated Starting date: Unknown

APPENDIX 4: CARDIOTOXICITY

Table 20. Cardiotoxicity − early breast cancer (FinHer)

Study ID	Adverse effect	Incidence of cardiotoxicity				Measurement and monitoring of cardiotoxicity
		Trastuzumab		No trastuzumab		
FINHER (10)	LVEF Median (range): no. Patients	**Docetaxel plus FEC and trastuzumab (n = 54)**	**Vinorelbine plus FEC and trastuzumab (n = 61)**	**Docetaxel plus FEC (n = 58)**	**Vinorelbine plus FEC (N = 58)**	**Monitoring** Echocardiography or isotope cardiography conducted before chemotherapy, after the last FEC cycle and 12 and 36 mo after chemotherapy
	▪ Before chemotherapy	66 (49−82): 50	64 (47−85): 61	67 (53−83): 56	65 (50−80): 53	**Cardiac status at baseline** Normal cardiac function required as eligibility criteria
	▪ At the last chemotherapy cycle	65 (51−78): 48	63 (47−85): 60	64 (48−78): 51	65 (46−80): 49	**Measurement used in the study**
	▪ 12 months after chemotherapy	66 (51−83): 48	65 (45−79): 60	64 (45−79): 49	65 (45−78): 48	Changes in LVEF measured by either ethnocardiography or isotope cardiography
	▪ 36 months after chemotherapy	69 (49−77): 30	64 (53-80): 32	64 (52−76): 24	63 (44−74): 22	A stated secondary outcome of the trial was the effect of treatment on the LVEF

Table 21. Cardiotoxicity − early breast cancer (studies except FinHer)

		Incidence of cardiotoxicity		
	Adverse effect	**Trastuzumab**	**No trastuzumab**	**Measurement and monitoring of cardiotoxicity**
HERA (11)	Evaluable	1677	1710	**Monitoring**
	Death from cardiac events (p=1.00)	0 (0%)	1 (0.06%)	Response to a cardiac questionnaire, physical examination,12 l4ead ECG, LVEF assessment by ethnocardiography or MUGA at baseline, 3,6,12,18,24,30,36, and 60 mo
	Severe CHF (p=0.002)	9 (0.54%)	0 (0%)	
	Symptomatic CHF, including severe CHF (p<0.001)	29 (1.73%)	1 (0.06%)	Cardiac safety analysis also conducted at 300, 600 and 900 patients who were followed for 6 mo. Any difference in incidence of CCF or cardiac death reviewed by a independent data monitoring committee used to cease or alter the trial
	Decrease in LVEF (p<0.001)	113 (7.08%)	34 (2.21%)	**Cardiac status at baseline**
				LVEF normal (≥55%) required as eligibility criterion
				Measurement used in the study
				Symptomatic CHF and an LVEF of 45% or less or a LVEF of <50% with an absolute reduction of 10% from baseline
NSABPB-31 (24, 55)	Evaluable	850	814	**Monitoring**
	Cardiac deaths	0	1	Cardiac history forms submitted at entry, every 6 mo for the first 5 yrs and yearly thereafter. MUGA scans in both arms before entry, after AC and at 6, 9 and 18 mo. Additional scans performed at the investigators discretion.
	Patients with confirmed CHF	31	4	
	▪ followed ≥ 6 mo from diagnosis of CHF	27	4	Cardiac review panel assessed all symptoms suggestive of CHF
	▪ reported symptoms during last 6 mo follow-up interval	1/27	1/1	Cardiac interim analysis after 200, 600 and 1,000 patients followed for 6 mo.
	▪ on medications during last 6 mo follow-up interval	18/27	1/1	**Cardiac status at baseline**
	Patients reporting cardiac dysfunction not meeting criteria for CHF	43	8	LVEF on multiple-gated acquisition (MUGA) scan ≥ lower limit of normal required as eligibility criteria. Patients with active cardiac disease, prior MI, CHF, cardiomyopathy excluded.
	▪ followed ≥ 6 mo from diagnosis of CD	39	6	
	▪ reported symptoms during last 6 mo follow-up interval	1/39	0/6	**Measurement used in the study**
	▪ on medications during last 6 mo follow-up interval	8/39	0/6	CHF (NYHAssociation class III or IV symptoms – decrease in baseline in LVEF of more than 10 percentage points to less than 55% or a decrease of > 5 percentage points to less than the LLN

		Incidence of cardiotoxicity		
	Adverse effect	**Trastuzumab**	**No trastuzumab**	**Measurement and monitoring of cardiotoxicity**
NCCTG-N9831 (25,55)	Cumulative incidence of NYHA class III or IV CHF or death from cardiac causes at 3 yrs	2.9%	0% 20 patients had CHF 1 patient died of cardiomyopathy	**Monitoring** Echocardiogram or multiple-gated acquisition (MUGA) at trial entry, 3 weeks after AC, 6 and 9 mo after registration and 3 mo after study completion Monthly meetings to review LVEF data and cardiac adverse events **Cardiac status at baseline** Normal LVEF required as eligibility criteria **Measurement used in the study** Left ventricular dysfunction, cardiac ischemia or arrhythmia LVEF decrease by 15% or by 15% or less to a level below the LLN National Cancer Institute Common Toxicity Criteria (version 2) was used to grade cardiac toxicity
Buzdar (14)	A greater than 10% decrease in the left ventricular ejection fraction	7/23	5/19	**Monitoring** Not reported **Cardiac status at baseline** Cardiac ejection fraction ≥ 45% required as eligibility criteria **Measurement used in the study** A greater than 10% decrease in the left ventricular ejection fraction

Table 22. Cardiotoxicity − metastatic breast cancer

Study ID	Adverse effect	Trastuzumab		No trastuzumab		Measurement and monitoring of cardiotoxicity
Slamon (16, 51)		**Trastuzumab + paclitaxel** (n=91)	**Trastuzumab +AC** (n=143)	**Paclitaxel alone** (n=95)	**AC alone** (n=135)	**Monitoring** Retrospective assessments by an independent cardiac evaluation committee of the incidence, severity, treatment and outcome of cardiac dysfunction using the NYHA in response to adverse cardiac events **Cardiac status at baseline** Not reported **Measurement used in the study** Decrease from baseline in LVEF of less than or equal to 5% to <55% with accompanying signs and symptoms of CHF or a decrease in LVEF of > or equal 10% to < 55% without signs and symptoms Note: 5 patients excluded who did not receive protocol-specified therapy (3 in AC, 1 in T+P, 1 in paclitaxel alone)
	▪ Cardiac dysfunction	12/91 (13%)	39/143 (27%)	1/95 (1%)	11/135 (8%)	
	▪ Class III or IV NYHA	2%	16%	1%	3%	

Assess-ments of TTP	All chemotherapy		Anthracycline plus cyclophosphamide		Paclitaxel	
	With trast (n=235)	Without trast (n=234)	With trast (n=143)	Without trast (n=138)	With trast (n=92)	Without trast (n=96)
TTP or any CD						
Median	6.6 mo	4.6 mo	6.6 mo	6.0 mo	6.6 mo	2.8 mo
95% CI	5.8−7.0 mo	4.4−5.3 mo	5.5−7.3 mo	4.8−6.9 mo	5.3−7.1 mo	2.0−4.3 mo
P value	0.0001		0.24		0.0001	
TTP or NYHA Class III/IV CD						
Median	7.0 mo	4.6 mo	7.2 mo	6.0 mo	6.9 mo	2.8 mo
95% CI	6.6−7.6 mo	4.4−5.4 mo	6.6−8.1 mo	4.9−7.1 mo	5.3−9.9 mo	2.0−4.3 mo
P value	0.0001		0.02		0.0001	
TTP or NYHA Class III/IV CD not improving to less than class III with cardiac treatment						
Median	7.2 mo	4.6 mo	7.6 mo	6.0 mo	6.9 mo	2.9 mo
95% CI	6.9−8.1 mo	4.4−5.4 mo	7.1−8.6 mo	4.9−7.1 mo	5.3−9.9 mo	2.0−4.3 mo
P value	0.0001		0.0019		0.0001	
NYHA Class III/IV CD-free survival time						
Median	22.2 mo	20.0 mo	22.3 mo	20.8 mo	22.1 mo	18.4 mo
95% CI	17.7− 25.4 mo	16.5− 23.9 mo	17.1− 26.3 mo	16.6− 25.7 mo	16.8− 28.6 mo	12.7− 24.4 mo
p value	0.52		0.78		0.19	

	Adverse effect	Trastuzumab + Docetaxel	Docetaxel alone	Measurement of cardiotoxicity
M77001	LVEF Worst Value (overall)			**Monitoring**
(18)	▪ Increase or no change	20%	33%	LVEF assessed by echocardiography or multiple gated acquisition scan every third cycle
	▪ Absolute decrease <15%	63%	60%	
	▪ Absolute decrease ≥ 15%	17%	8%	LVEF monitoring ceased in patients receiving docetaxel alone after completion of therapy. However, LVEF monitoring continued throughout trastuzumab treatment in the combination arm.
	▪ Absolute value < 40%	1%	0%	
				Cardiac status at baseline
	LVEF Worst Value (up to cycle 6)			LVEF >50% required as eligibility criteria
	▪ Increase or no change	41%	41%	**Measurement used in the study**
	▪ Absolute decrease <15%	48%	54%	Decrease in LVEF
	▪ Absolute decrease ≥ 15%	11%	6%	CHF
	▪ Absolute value < 40%	1%	0%	

APPENDIX 5: EARLY PHASE CLINICAL TRIALS

Table 23. Trastuzumab as neoadjuvant therapy

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Mohsin (56)	2005	35	Phase II	35	1999−2003	Not reported	Locally advanced Cardiac function not reported	Positive = IHC 3+ *or* ≥ 5 by Allred system *or* FISH+	Not reported	**Trastuzumab + docetaxel (neoadjuvant):** Trastuzumab loading dose 4 mg/ m^2 then 2 mg/m^2 weekly On day 22 trastuzumab followed by docetaxel 100 mg/m^2 every 3 wks for 4 cycles	• Tumour regression prior to surgery
Wenzel (57)	2004	38	Phase II	14	2000−2001	Not reported	Primary breast cancer T2−T4 LVEF > 50%	Positive = IHC 3+ *or* IHC 2+ and FISH +	Not reported	**Trastuzumab + epidoxorubicin + docetaxel (neoadjuvant):** Trastuzumab initially 4 mg/kg as loading dose then 2 mg/kg; epidoxorubicin 30 mg/m^2; docetaxel 35 mg/m^2 Treatment once a wk for 6 wks, then 1 wk off, for at least 2 cycles until best response judged	• Response • Toxicity
Burstein (58)	2003	79	Phase II	40	1999−2000	Median 25 mo (9−37)	Early (pre-operative) LVEF ≥ 50%	Positive = IHC 3+ *or* IHC 2+	Excluded patients receiving prior anthracycline or taxane-based chemotherapy, or prior high-dose chemotherapy with stem cell transplant	**Trastuzumab + paclitaxel -> surgery -> doxorubicin + cyclophosphamide (neoadjuvant):** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly for 11 wks; paclitaxel 175 mg/m^2 q3 weeks for 4 cycles; Surgery; Adjuvant doxorubicin and cyclophosphamide at standard doses for at least 6 wks	• **Pathologic complete response** • Clinical response • Distant disease-free survival • Recurrence • Effect on HER2 status • Toxicity

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Coudert (59)	2006	229	Phase II	33	2001−2003	Median 26 months	Stage II/III non-inflammatory operable breast cancer LVEF normal	Positive = IHC 3+	No previous chemotherapy allowed	**Trastuzumab + Docetaxel (neoadjuvant):** Trastuzumab 4 mg/kg then 2 mg/kg weekly; docetaxel 100 mg/kg 3-weekly for 6 cycles	• Safety & tolerability • Complete & partial response rates • Levels of breast-conserving surgery • Disease-free survival • Local & distant relapses

Table 24. Trastuzumab alone for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Tokuda (60)	1999	96	Phase I	18	Not reported	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC where at least 10% of tumour cells had positive membrane staining	Refractory to conventional (doxorubicin-containing) chemo or endocrine therapies	**Trastuzumab (single agent):** Trastuzumab starting dose 1 mg/kg, with subsequent dose escalations to 2, 4 and 8 mg/kg^{-1}.	• Response • Toxicity
Baselga (40)	2005	37	Phase II	105	Not reported	Not reported	Metastatic LVEF ≥ 50% excluded	Positive = IHC 3+ *and/or* FISH+	Prior neo/adjuvant 1^{st} line for metastatic disease Previous treatment with cumulative dose of doxorubicin > 480 mg/m^2 or epirubicin 800 mg/m^2 excluded	**Trastuzumab (single agent):** Trastuzumab loading dose 8 mg/kg then 6 mg/kg 3 weekly until disease progression or toxicity	• Response • Time to progression • Toxicity • Cardiac safety (changes in LVEF, hypertension and tachycardia) • Pharmaco-kinetics and pharmaco-dynamics
Baselga (61)	1999	94	Phase II	46	Not reported	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC where at least 25% of the tumour cells exhibited characteristic membrane staining for $p185^{HER2}$	No chemotherapy 3 weeks before study entry allowed.	**Trastuzumab (single agent):** Trastuzumab 250 mg on day 0 then 100 mg weekly for a total of 10 doses. Responders received maintenance Trastuzumab weekly	• Response • Toxicity

Table 25. Trastuzumab plus taxanes for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Julka (62)	2004	53	Phase II	16	Not reported	Not reported	Metastatic LVEF ≥50%	Positive = IHC 3+	No previous chemotherapy or anthracyclines (not specified if for early or metastatic disease)	**Trastuzumab + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Docetaxel 100 mg/m^2 q3/52	• Response • Toxicity
Montemurro (63)	2004	54	Phase II	42	1999−2002	Median 14 months (3−38 mo)	Metastatic, or locally advanced having failed at least 1 line of chemotherapy LVEF ≥ 50%	Positive = IHC 3+ or 2+	Allowed up to 2 prior chemotherapy regimens for advanced disease. Prior anthracycline and paclitaxel allowed. No prior docetaxel allowed.	**Trastuzumab + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Docetaxel 75 mg/m^2 q3/52	• Response • Progression-free survival • Toxicity • Time to treatment failure • Duration of response • Survival
Tedesco (64)	2004	56	Phase II	26	1999−2001	Not reported	Metastatic LVEF ≥ 45%	Positive = IHC 2+ or 3+	No more than one chemotherapy regimen for metastatic disease. Total dose of prior doxorubicin <250 mg/m^2; no prior taxanes.	**Trastuzumab + Docetaxel:** Trastuzumab initially 4 mg/ kg then 2mg/kg weekly Docetaxel 35 mg/m^2 weekly for 6 wks 8 wk cycles	• Response • Time to progression • Survival • Toxicity
Montemurro (65)	2003	78	Phase II	25	1999-2001	Not reported	Metastatic LVEF ≥ 50%	Positive = IHC 3+ *or* IHC 2+ of more than 10% of tumour cells	Prior treatment with up to 2 chemotherapy regimens for MBC allowed. Prior anthracycline and/or paclitaxel allowed.	**Trastuzumab + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Docetaxel 75 mg/m^2 After 6 cycles responding patients received trastuzumab 2 mg/kg weekly	• **Response** • Toxicity

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Esteva (66)	2002	83	Phase II	30	?	Not reported	Metastatic LVEF ≥ 50%	Positive = IHC (not defined) and FISH+	Prior treatment with up to 3 chemotherapy regimens for adjuvant, neoadjuvant or MBC allowed. Prior trastuzumab not allowed. Previous taxane allowed if more than 1 yr before enrolment.	**Trastuzumab + docetaxel:** Trastuzumab initially 4mg/kg then 2mg/kg weekly Docetaxel 35 mg/m^2 Both in 4-wk cycles (3 weekly treatments followed by 1 wk of rest)	• Response • Toxicity • Time to progression • Delivered dose intensity
Raff (67)	2004	55	Phase II	53	1997−2002	Not reported	Metastatic LVEF normal	Positive = IHC 2+ or 3+	Allowed to have received any amount of prior chemotherapy	**Trastuzumab + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly modified to 4 mg/kg loading dose then 2 mg/kg days 1, 8, 15 and then q28 days Docetaxel 33 mg/m^2 weekly modified to 40 mg/m^2 days 1, 8, 15 and then q28 days Note: compared docetaxel + trastuzumab in HER2 positive with docetaxel alone in HER2 negative	• Toxicity • Response • Time to progression • Survival
Christodoulou (22)	2003	76	Phase II	26	1998−2001	Median 52 months	Metastatic LVEF ≥ 50%	Positive = where weak to strong membrane staining in at least 25% of the tumour cells	Any number, including anthracyclines and/or taxanes. No prior trastuzumab.	**Trastuzumab + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Paclitaxel 90 mg/kg (if firstline chemotherapy for metastatic disease, 70 mg/kg if secondline) after trastuzumab weekly	• **Response** • Time to progression • Survival • Toxicity

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Fountzilas (68)	2001	85	Phase II	34	1998−2000	Median 14.4 mo (4.6−24.5)	Metastatic LVEF ≥ 50%	Positive = where weak to strong membrane staining in at least 25% of the tumour cells	No previous chemotherapy for MBC	**Trastuzumab + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Paclitaxel 90 mg/m^2 weekly for at least 12 wks	• **Response** • Toxicity • Time to progression • Survival • Response duration
Seidman (69)	2001	90	Phase II	95	Not reported	Not reported	Metastatic LVEF ≥ 50%	Normal or positive Positive = IHC 2+ or 3+ *or* FISH+	Prior treatment with up to 3 chemotherapy regimens for adjuvant, neoadjuvant or MBC allowed. Prior trastuzumab not allowed. Previous anthracycline allowed. Previous taxane allowed if more than 1 yr since last exposure	**Trastuzumab + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Paclitaxel 90 mg/m^2	• Response • Toxicity
Gori (70)	2004	59	Phase II	25	1999-2001	Median 19.6 mo (9.2−38.1)	Metastatic LVEF normal	Positive = IHC weak to strong membrane staining in ≥ 60% of neoplastic cells	Anthracycline and taxane pre-treated	**Trastuzumab + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Paclitaxel 60−90 mg/m^2 weekly	• Response • Response duration • Toxicity • Time to progression

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Leyland-Jones (39)	2003	65	Phase II	32	Not reported	All patients completed at least one year of follow-up	Metastatic LVEF > 50%	Positive = IHC 2+ or 3+ *or* FISH+	No prior chemotherapy with taxanes for metastatic disease	**Trastuzumab + paclitaxel:** Trastuzumab initially 8 mg/kg then 6 mg/kg Paclitaxel 170 mg/m^2 Both q 3 weeks for 7 cycles Responders received Trastuzumab monotherapy q 2 weeks until progression	• **Pharmacokinetics** • **Safety** • Response

Table 26. Trastuzumab plus platinum for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Pegram (71)	1998	97	Phase II	37	Not reported	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC 2+ or 3+	Documentation of objective progression while receiving active chemotherapy. No chemotherapy 3 wks before study entry allowed	**Trastuzumab + cisplatin:** Trastuzumab 250 mg loading dose then 100 mg weekly for a total of 8 doses Cisplatin 75 mg/m^2 day 1, 29 and 57 Responders received maintenance Trastuzumab 100 mg weekly plus cisplatin 75 mg/m^2 q4 wks	• Response • Response duration • Toxicity
Pegram (72)	1999	93	Phase I/II	15+37	Not reported	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC 2+ or 3+	Not reported	**Trastuzumab + cisplatin:** Trastuzumab 250 mg on day 0 then 100 mg weekly for 8 doses Cisplatin 75 mg/m^2 day 1, 29 and 57	• Response • Response duration • Toxicity

Table 27. Trastuzumab plus platinum plus other agents for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Nieto (23)	2004	42	Phase 2	33	1999−2003	Median 34 months (13−58)	Advanced 13/33 high risk stage 2−3 20/33 MBC LVEF > 45% at rest and at least 5% augmentation on exercise	Positive = initially IHC 2+ or 3+ amended during study to IHC 3+ *or* 2+ and FISH+	Previous adjuvant chemotherapy – no prior HDC or cumulative anthracycline exposure	**Trastuzumab + cisplatin + cyclophosphamide + BCNU:** Trastuzumab initially 4 mg/kg then 2 mg/kg/week Cisplatin 165 mg/m^2 Cyclophosphamide 1875 mg/m^2/day for 3 days BCNU 600mg/m^2	• Response • Overall survival • Toxicity • Cardiac toxicity • Pharmaco-kinetics

Table 28. Trastuzumab plus taxanes plus platinum for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Pegram (b) BCIRG 101 (73)	2004	49	Phase II	62	1999–2000	Not reported	Metastatic Stage IIIB or IV Normal LVEF	Positive = IHC 3+ *or* 2+ and FISH+	BCIRG 101: previous adjuvant chemotherapy no metastatic (21 anthracycline)	**Trastuzumab + docetaxel + cisplatin:** Trastuzumab initially 4 mg/kg then 2 mg/kg Docetaxel 75 mg/m^2 Cisplatin 75 mg/m^2 21 day cycle for 1 yr or until disease progression	• Tumour Response • Toxicity • Safety • Cardiac toxicity • Time to progression • Overall survival
Pegram (a) UCLA-ORN (73)	2004	49	Phase II	62	1999−2000	Not reported	Metastatic Stage IIIB or IV Normal LVEF	Positive = IHC 3+ *or* 2+ and FISH+	UCLA- ORN: previous adjuvant/neoadjuvant and metastatic CT (28 anthracycline; 9 taxanne)	**Trastuzumab + docetaxel + carboplatin:** Trastuzumab initially 4 mg/kg then 2 mg/kg Docetaxel 75 mg/m^2 Carboplatin AUC 6 mg/mL 21 day cycle for 1 yr or until disease progression	• Tumour Response • Toxicity • Safety • Cardiac toxicity • Time to progression • Overall survival
Perez (a) (74)	2005	28	Phase II	43	1999-2003	Minimum 9 mo	Metastatic Cardiac function of included participants not reported Those with uncontrolled or severe cardiac disease excluded	Positive = ICH 3+ *or* FISH+	No previous chemotherapy for metastatic disease. Previous adjuvant therapy permitted including taxanes but no previous cisplatin or carboplatin	**Trastuzumab + paclitaxel + carboplatin:** Paclitaxel 200 mg/m^2 day 1 Carboplatin AUC 6 mg/mL/min Trastuzumab 4 mg/kg day 1 then 2 mg/kg days 8 and 15. Trastuzumab modified August 2002 to 8 mg/kg day 1 cycle 1, then 6 mg/kg day 1 of subsequent cycles Repeated every 21 days for a maximum of 8 cycles.	• Overall survival • Progression free survival • Tumor response rates • Toxicity • Time to progression • Time to treatment failure • Duration of response

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Perez (b) (74)	2005	28	Phase II	48	1999-2003	Minimum 9 mo	Metastatic Cardiac function of included participants not reported Those with uncontrolled or severe cardiac disease excluded	Positive = ICH 3+ *or* FISH+	No previous chemotherapy for metastatic disease. Previous adjuvant therapy permitted including taxanes but no previous cisplatin or carboplatin	**Trastuzumab + paclitaxel + carboplatin:** Paclitaxel 80 mg/m^2 days 1, 8 and 15 Carboplatin AUC 2 mg/mL/min days 1, 8 and 15 Trastuzumab 4 mg/kg on day 1 then 2 mg/kg days 8, 15 and 22 Treatment repeated for a maximum of 6 (4 wk) cycles After 6 m of combined therapy, patients received Trastuzumab alone initially weekly 2mg/kg, later amended to 6mg/kg administered every 3 weeks	• Overall survival • Progression free survival • Tumor response rates • Toxicity • Time to progression • Time to treatment failure • Duration of response
Burris (75)	2004	51	Phase II	61	1998-2001	To Jan 2004	Metastatic LVEF normal	Positive = IHC 2+ or 3+	No previous chemotherapy for metastatic disease. Allowed one prior adjuvant or neoadjuvant chemotherapy regimen. Adjuvant taxane allowed if q 3/52 (not weekly). Prior trastuzumab and adjuvant doxorubicin doses more than 360 mg/m^2 not allowed.	**Trastuzumab + paclitaxel + carboplatin:** Trastuzumab initially 8 mg/kg then 4 mg/kg weekly for 8 wks *Responders* received additional 4 mg/kg/wk for 8 wks, then 2 mg/kg plus paclitaxel and carboplatin weekly for 6 wks *Stable* after first 8 wks received weekly trastuzumab, paclitaxel and carboplatin *Disease progression* during first 8 wks received weekly paclitaxel and carboplatin	• Response • Time to progression • Overall survival • Dose modifications • Treatment-related toxicity (haematologic, non-haematologic and cardiac)

Table 29. Trastuzumab plus anthracycline with or without other agents for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Lunardi (76)	2003	69	Phase I	8	Not reported	Not reported	Metastatic LVEF normal	Positive = IHC 2+ or 3+	Not mentioned	**Trastuzumab + epirubicin + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly until progresson Epirubicin 75 mg/m^2 and Docetaxel 75 mg/m^2 both q 3 weeks for 6 cycles	• Pharmacokinetics
Bianchi (77)	2003	63	Phase 2	2 trials x 16 patients	Cohort 1 1999−2000 Cohort 2 2000−2001	Cohort 1 median 86.9 wks Cohort 2 median 57.4 wks	Stage IIIB/IV LVEF > 50%	Cohort 1 Positive = IHC 2+ or 3+ Cohort 2 Positive = IHC 3+ *or* FISH+	No previous chemotherapy for advanced disease; no prior anthracyclines	**Trastuzumab + doxorubicin + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Doxorubicin 60 mg/m^2 day 1, and Paclitaxel 150 mg/m^2 day 1 Both q 3 wks for 3 cycles, then 9 cycles of weekly paclitaxel 80 mg/m^2	• Safety • Response • Time to progression • Overall survival • Pharmacokinetics
Venturini (78)	2006	234	Phase II	45	7/2000−12/2001	Not reported	Metastatic LVEF ≥ 50%	Positive = IHC 2+ or 3+	1st line for metastatic disease, prior doxorubicin or docetaxel therapy (regardless of dose) or prior epirubicin to a cumulative dose >360 mg/m^2 as adjuvant treatment excluded.	**Trastuzumab + epirubicin + docetaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Chemotherapy: epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2 Both on day 1 of a 3 weekly cycle	• Cardio-toxicity • response • time to progression • Adverse events/

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Untch (79)	2004	39	Phase I/II	51 Dose 1 26 pts Dose 2 25 pts Control 23 pts (HER2 negative)	Not reported	4−6 mo at time of report	Metastatic LVEF ≥ 45%	Positive = IHC 3+ or FISH+ Control arm HER2 negative	No prior anthracycline therapy or high dose chemotherapy with stem cell transplant – no prior chemotherapy for MBC	**Trastuzumab + epirubicin + cyclophosphamide:** Trastuzumab 2 mg/kg Epirubicin 60 mg/m^2 (Dose 1) Cyclophosphamide 600 mg/m^2 If cardiotoxicity acceptable, epirubicin escalated to 90 mg/m^2 (Dose 2) HER2 neg patients received EC90 alone Administered for 6 x 3 wk cycles	• Cardiac function and adverse events (LVEF) • Response • Toxicity
Untch (80)	2004	52	Phase I/II	75	2000−2002	1 yr post chemo-therapy	Metastatic LVEF <55%	Positive = IHC 3+ and/or FISH positive	No previous chemotherapy for metastatic disease. No prior anit-HER2 treatment No prior anthracyclines or high dose chemotherapy with PBSC transplantation	**Trastuzumab + epirubicin and cyclophosphamide:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Epirubicin 60 (then 90) mg/m^2 Cyclophosphamide 600 mg/m^2 Note: compared EC + Trastuzumab in HER2 positive with EC alone in HER2 negative	• Cardiac safety • Other safety • Response NOTE: Aim was to identify an anthracycline-containing combination with acceptable dose-limiting cardiotoxicity

Table 30. Trastuzumab plus gemcitabine for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Czejka (81)	2005	34	Phase II	8	Not reported	Not reported	Advanced Cardiac function not reported	Positive = IHC 3+	Not reported	**Trastuzumab + gemcitabine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Gemcitabine 1000 mg/m^2 day 1	• Pharmaco-kinetics
O'Shaughnessy (45)	2004	46	Phase II	64	1999-2001	Not reported	Metastatic LVEF normal	Positive = IHC 2+ or 3+	56/64 Prior adjuvant.CT. 61 pts had received 3 or less CT for MBC. No prior treatment by gemcitabine or trastuzumab	**Trastuzumab + gemcitabine:** Trastuzumab initially 4 mg/kg then 2 mg/kg/week Gemcitabine 1200 mg/m^2 weekly for 2 wks 21-day cycle until disease progression	• Response • Efficacy • Toxicity • Time to Progression • Overall survival
O'Shaughnessy (82)	2003	75	Phase II	64 (reports preliminary results on 38 patients in this paper)	Not reported	Not reported	Metastatic LVEF normal	Positive = IHC 2+ or 3+	Up to 3 prior chemotherapy regimens permitted No prior Trastuzumab or gemcitabine allowed	**Trastuzumab + gemcitabine:** Trastuzumab initially 4 mg/kg (on day 8) then 2 mg/kg weekly Gemcitabine 1,200 mg/m^2 days 1 and 8 of each 21 day cycle. Both agents continued until disease progression	• Response • Response duration • Time to progression • Overall survival • Toxicity
O'Shaughnessy (83)	2002	81	Phase II (preliminary results)	38+	1999−?	Not reported	Metastatic LVEF normal	Positive = IHC 2+ or 3+ *or* FISH+	Prior treatment with up to 3 chemotherapy regimens for MBC allowed. Prior gemcitabine and/or trastuzumab not allowed.	**Trastuzumab + gemcitabine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Gemcitabine 1200 mg/m^2 days 1 and 8 of each 21 day cycle	• Response • Response duration • Time to progression • Overall survival • Toxicity

Table 31. Trastuzumab plus gemcitabine plus taxane for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Miller (84)	2001	91	Phase II (preliminary results)	27	1999−2000	Not reported	Locally recurrent or Metastatic "Adequate" cardiac function	Positive = IHC 2+ or 3+ *or* FISH+	No prior chemotherapy for advanced disease. Previous taxanes permitted if completed ≥ 6 mo before study entry	**Trastuzumab + paclitaxel + gemcitabine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Paclitaxel 175 mg/m^2 day 1 Gemcitabine 1,200 mg/m^2 days 1 and 8 Every 21 days for 6 cycles	• **Response** • Toxicity • Time to progression • Overall survival
Fountzilas (85)	2004	40	Phase II	40	2000-2002	Median 12.2 mo (0.56−23)	Advanced LVEF ≥ 50%	Positive = ICH 3+ or FISH+	Previous adjuvant chemotherapy allowed if interval from completion to 1st recurrence ≥ 12 mo	**Trastuzumab + paclitaxel + gemcitabine:** Trastuzumab initially 4 mg/kg then 2 mg/kg/wk Paclitaxel 80 mg/m^2/wk Gemcitabine 1000 mg/m^2 every 2 wks For 12 wks	• Response • Time to progression • Toxicity
Sledge (86)	2003	60	Phase II	45	Not reported	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC 2+ or 3+, *or* FISH+	No prior chemotherapy for metastatic disease; no prior gemcitabine or trastuzumab	**Trastuzumab + gemcitabine + paclitaxel:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Gemcitabine 1,200 mg/m^2 days 1 and 8 Paclitaxel 175 mg/m^2 day 1 For 6 x 21 day cycles	• Toxicity • Response

Table 32. Trastuzumab plus gemcitabine plus platinum for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Stemmler (87)	2005	30	Phase II	20	2001−2004	Not reported	Metastatic Normal Cardiac ejection fraction required for inclusion	Positive = IHC 3+	Prior adjuvant chemotherapy (taxanes, anthracyclines, taxanes + trastuzumab) 12/20 had received up to 5 prior CT regimens for MBC	**Trastuzumab + gemcitabine + cisplatin:** Trastuzumab initially 2 mg/kg then 4 mg/kg weekly Gemcitabine 750 mg/m^2, and Cisplatin 30 mg/m^2 days 1 and 8 of a 3 week cycle Treatment continued until disease progression or unacceptable toxicity	• Efficacy and tolerability • Overall survival • Time to disease progression • Response

Table 33. Trastuzumab plus vinorelbine for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Burstein (42)	2003	68	Phase II	55	2000−2001	On-study median 5.6 mo ().46−16 months)	Metastatic LVEF ≥ 50%	Positive = IHC 3+ *or* FISH+	No prior chemotherapy for metastatic disease, or prior vinorelbine. Cumulative doxorubicin not more than 360 mg/m^2	**Trastuzumab + vinorelbine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Vinorelbine 25 mg/m^2 weekly	• **Response** • Toxicity • Time to treatment failure
Jahanzeb (43)	2002	80	Phase II	40	1999−2001	Not reported	Metastatic\ LVEF ≥ 50%	Positive = IHC 2+ or 3+ *or* FISH+	No prior chemotherapy for MBC	**Trastuzumab + vinorelbine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Vinorelbine 30 mg/m^2 weekly	• Response • Toxicity • Time to progression • Overall survival
Burstein (41)	2001	89	Phase II	40	1998−1999	Not reported	Metastatic LVEF ≥ 50%	Positive = IHC 2+ or 3+	Originally prior treatment with at least one and no more than 2 chemotherapy regimens for MBC allowed. Expanded to include women who had not received chemotherapy for MBC. No prior vinorelbine or trastuzumab	**Trastuzumab + vinorelbine:** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Vinorelbine 25 mg/m^2 weekly	• **Response** • Time to progression • Overall survival • Toxicity

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Papaldo (44)	2006	225	Phase II	68	2000−2004	Median 17 mo (1−43)	Metastatic LVEF ≥ 50%	Positive = IHC 3+ *or* IHC 2+ and FISH+	Had received at least one prior chemotherapy regimen for metastatic breast cancer. No prior vinorelbine	**Trastuzumab + vinorelbine:** Trastuzumab initially 4 mg/kg then 2mg/kg weekly Vinorelbine 25 mg/m^2 weekly Note: HER2 negative treated with vinorelbine alone; HER2 positive treated with vinorelbine and trastuzumab	• Overall response • Time to progression • Overall survival • Cardiac function • Toxicity

Table 34. Trastuzumab plus other agents for advanced breast cancer

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Repka (88)	2003	72	Phase I	10	Not reported	Not reported	Metastatic LVEF >40%	Positive = IHC 2+ or 3+	No restrictions	**Trastuzumab + interleukin-2:** Trastuzumab initially 4 mg/kg (on day 8) then 2 mg/kg weekly for 6 doses Interleukin-2 1.75 x 10^6 iu/m^2/day x 49 days	• **Toxicity** • Response
Tokuda (89)	2001	86	Phase II	41	1999−2001	Not reported	Metastatic Cardiac function not mentioned	Positive = IHC 2+ or 3+	Not described	**Trastuzumab + "chemotherapy":** Trastuzumab initially 4 mg/kg then 2 mg/kg weekly Chemotherapy: some patients also given paclitaxel, docetaxel, vinorelbine, cyclophosphamide or 5'DFUR	• Response • Toxicity
Dang (46)	2004	47	Phase II	12	2000−2002	Not reported	Metastatic LVEF > 50%	Positive = IHC 2+ or 3+	Any number or type of prior cytotoxic therapy allowed in adjuvant/ neoadjuvant or metastatic setting	**Trastuzumab + Celecoxib (NSAID):** Trastuzumab 2 mg/kg (loading dose 6 mg/kg if not received previously or if 2 wks since last treatment) Celecoxib 400 mg orally twice a day	• Response • Efficacy • Safety • Toxicity
Walshe (48)	2006	218	Phase II (ongoing)	Target accrual not reported	Not reported	Not reported	Locally advanced and metastatic LVEF normal	Positive = FISH+	No previous chemo/immunotherapy for MBC weekly treatment within 7 days for those on weekly treatment , nor within 3 wks on other time schedules. No previous chemotherapy for locally advanced BC.	**Trastuzumab + pertuzumab** Dependent on time between previous administration and cardiology evaluation	• Objective response rate • safety • TTP • survival

First author	Year pub	Ref ID	Study design	No. pts	Years accrued	Follow-up details	Stage of disease & cardiac function	HER2 status	Prior chemotherapy	Treatment details	Outcomes
Moulder (47)	2003	70	Phase I/II	Open to recruitment	2003− ?	Not reported	Metastatic LVEF ≥ 50%	Positive = IHC 3+ *or* IHC 2+ and FISH+	Exclude prior Trastuzumab or gefitinib, more than 2 prior chemotherapy regimens for metastatic disease, history of chemotherapy 2 wks prior to registration, cumulative dose of doxorubicin > 360 mg/m^2	**Trastuzumab + gefitinib:** Trastuzumab: loading dose 4 mg/kg then 2 mg/kg weekly Gefitinib 250 mg po daily Note: Design paper. No results reported	No results available

APPENDIX 6: NHMRC HIERARCHY OF EVIDENCE (90)

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time-series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case-series, either post-test or pre-test/post-test.

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ABBREVIATIONS

Acronym	Definition
ARR	Absolute risk reduction
ASCO	American Society for Clinical Oncology
BCIRG	Breast Cancer International Research Group
CALGB	Cancer and Leukemia Group B
CBCG	Cochrane Breast Cancer Group
CD	Cardiac dysfunction
CHF	Congestive heart failure
CI	Confidence interval
CR	Complete response
ER	Oestrogen receptor
FISH	Fluorescence in situ hybridization
GBC	Gestational breast cancer
HER2	Human epidermal growth factor receptor 2
HR	Hazard ration
HTA	Health Technology Assessment
IHC	Immunohistochemistry
LVEF	Left Ventricular Ejection Fraction
Mo	Month
NBCC	National Breast Cancer Centre
NCRI	National Cancer Research Institute
NHS R&D	National Health Service Research and Development
NICE	National Institute for Clinical Excellence
NLM	National Library of Medicine
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New York Heart Association
PABC	Pregnancy associated breast cancer
pCR	Pathologic complete response
PR	Progesterone receptor
Wk	Week
Yr	Year