

RECOMMENDATIONS FOR USE OF

Trastuzumab (Herceptin®)

for the treatment of HER2-positive breast cancer

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY THE NATIONAL BREAST CANCER CENTRE (NBCC)

This document supplements guideline recommendations on systemic adjuvant therapy, contained in the NBCC *Clinical Practice Guidelines for the Management of Early Breast Cancer*, 2nd edition, 2001;¹ and guideline recommendations on the management of metastatic disease, contained in the NBCC *Clinical Practice Guidelines for the Management of Advanced Breast Cancer*, 2nd edition, 2001.²

PURPOSE

To provide statements and recommendations based on the best available evidence, about the use of trastuzumab (Herceptin®) as adjuvant therapy for the treatment of patients with HER2-positive early breast cancer and for the treatment of patients with HER2-positive metastatic breast cancer. For information on the Pharmaceutical Benefits Scheme (PBS) listing for Herceptin® please see page 21 of this guideline.

Endorsed by:



The Royal Australasian
College of Physicians



BACKGROUND

Trastuzumab is a monoclonal antibody which targets breast cancer cells that over-express the HER2 protein. Approximately 20%³ of newly diagnosed breast cancers have HER2 gene amplification, leading to over-expression of the HER2 protein. HER2 over-expression is associated with adverse prognostic factors including large nuclear size, high nuclear grade, and decreased expression of oestrogen and progesterone hormone receptors, together with reduced disease-free and overall survival for patients with node-positive or node-negative breast cancer. By binding to HER2 protein receptors, trastuzumab interrupts the growth signal, thereby slowing the growth and spread of breast cancer cells. For information on HER2 testing see page 15 of this guideline.

EVIDENCE

Use of trastuzumab as adjuvant therapy for HER2-positive early breast cancer

This clinical practice guideline is based on available evidence from six randomised trials (five adjuvant and one neoadjuvant) assessing the use of trastuzumab in the treatment of HER2-positive early breast cancer:

- four trials randomised patients to adjuvant trastuzumab with chemotherapy (BCIRG 006;⁴ FinHer;⁵ NCCTG-N98316;⁶ NSABP-B31⁶)
- one trial randomised patients to adjuvant trastuzumab after chemotherapy (HERA^{7,8})
- one trial randomised patients to neoadjuvant trastuzumab with chemotherapy (Buzdar⁹).

(see table 1 on page 11 for trial details)

Data from two trials (NCCTG-N9831 and NSABP-B31) were reported in a combined data analysis. Five randomised trials of adjuvant trastuzumab showed an improvement in disease-free survival and three showed improvements in overall survival in women with HER2-positive early breast cancer. One trial of neoadjuvant trastuzumab showed an improvement in pathologic complete response (pCR) rate. See page 12 for more result details.

The scheduling of trastuzumab (weekly or 3-weekly) did not appear to affect treatment outcome, although a direct comparison of the two regimens has not been reported. While an overall survival benefit has been demonstrated using trastuzumab for 1 year, either sequentially or concurrently with chemotherapy, the optimal duration and sequence of administration of trastuzumab is unknown.

All four adjuvant trials reported a decline in cardiac function associated with trastuzumab (both symptomatic and asymptomatic). The risk of congestive heart failure was reduced when trastuzumab was given with non-anthracycline-based chemotherapy. The long-term side effects of trastuzumab are not yet known.

Use of trastuzumab for HER2-positive metastatic breast cancer

This clinical practice guideline is based on available evidence from six randomised trials assessing the use of trastuzumab in the treatment of HER2-positive metastatic breast cancer:

- three trials compared chemotherapy alone with chemotherapy plus trastuzumab (Gasparini;¹⁰ M77001;¹¹ Slamon¹²)
- two trials compared trastuzumab-containing regimens (BCIRG 007;¹³ Vogel^{14,15})
- one trial started randomising HER2-positive and negative patients to chemotherapy with or without trastuzumab but ceased randomisation in HER2-positive patients after publication of other trial data (CALGB 9840¹⁶).

(see table 2 on page 13 for trial details)

Two of the trials that compared chemotherapy alone with chemotherapy plus trastuzumab showed an improvement in progression-free survival and an improvement in overall survival in women with HER2-positive metastatic breast cancer. See page 14 for more result details.

No trials have reported direct comparisons of different trastuzumab regimens. The trials that demonstrated a benefit of trastuzumab with chemotherapy used a weekly dose of trastuzumab. No trials have evaluated the optimal duration of treatment; trastuzumab was used until disease progression or unacceptable toxicity. Two trials reported a decline in cardiac function associated with trastuzumab (in combination with an anthracycline and cyclophosphamide or with docetaxel).

STATEMENTS AND RECOMMENDATIONS

| STATEMENTS | LEVEL OF EVIDENCE ^{17*} | TRIAL AND REFERENCE |
|--|----------------------------------|---|
| In women with HER2-positive early breast cancer following surgery: | | |
| Combination with chemotherapy | | |
| The addition of adjuvant trastuzumab to adjuvant chemotherapy improves disease-free and overall survival compared to adjuvant chemotherapy alone in women with node-positive or node-negative primary tumours larger than 1 cm | II | BCIRG 006; ⁴ HERA; ⁷ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |
| No trials have examined the benefit of adjuvant trastuzumab in women with node-negative primary tumours 1 cm or smaller | | |

| STATEMENTS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|--|-------------------|--|
| Single-agent trastuzumab | | |
| There are no data regarding use of single-agent adjuvant trastuzumab without prior chemotherapy | | |
| Combination with systemic therapies other than chemotherapy | | |
| There are no data from randomised trials about the use of adjuvant trastuzumab with non-chemotherapy systemic therapies in the absence of prior treatment with chemotherapy drugs | | |
| Combination with radiotherapy | | |
| A non-randomised subgroup analysis of one randomised trial has shown no increased toxicity with adjuvant trastuzumab in patients receiving concurrent adjuvant radiotherapy after 1.5 years of follow-up | III | NCCTG-N9831 ¹⁸ |
| Optimal dose, schedule and duration of administration | | |
| Overall survival benefit has been demonstrated in studies that used trastuzumab for 1 year | II | HERA; ^{7,8} NCCTG-N9831; ⁶ NSABP-B31 ⁶ |
| An ongoing randomised trial is comparing adjuvant trastuzumab use for 1 year versus 2 years | | |
| Relapse-free survival benefit has been shown in one small phase III study using trastuzumab for 9 weeks concurrently with vinorelbine or docetaxel | II | FinHer ⁵ |
| Weekly (loading dose of 4 mg/kg then 2 mg/kg) and 3-weekly (loading dose of 8 mg/kg then 6 mg/kg) dosing is effective; no direct comparison of weekly and 3-weekly schedules is available | II | FinHer; ⁵ HERA; ⁷ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |

| STATEMENTS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|--|-------------------|--|
| Randomised trials have used adjuvant trastuzumab concurrently and sequentially with chemotherapy | II | FinHer; ⁵ HERA; ⁷ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |
| A randomised comparison of adjuvant trastuzumab sequential to, or concurrent with adjuvant chemotherapy is ongoing | | NCCTG-N9831 ¹⁹ |
| In women with HER2-positive locally advanced or inflammatory breast cancer: | | |
| A phase II study suggests that use of trastuzumab with preoperative chemotherapy in locally advanced or inflammatory breast cancer is safe and feasible | III | Hurley ²⁰ |
| In women with HER2-positive breast cancer undergoing preoperative chemotherapy: | | |
| The use of trastuzumab following neoadjuvant chemotherapy and surgery shows improved progression-free survival in women with breast cancers that are 2–5 cm in size | II | HERA ⁷ |
| There is evidence from a small randomised phase III trial that adding concurrent trastuzumab to preoperative chemotherapy increases the proportion of women obtaining pathologic complete response (pCR) | II | Buzdar ⁹ |
| In women with HER2-positive metastatic breast cancer: | | |
| Combination with systemic therapies | | |
| Trastuzumab in combination with chemotherapy leads to superior response and improved progression-free survival and overall survival compared with chemotherapy alone | II | M77001; ¹¹ Slamon ¹² |
| Trastuzumab combined with a taxane (either docetaxel or paclitaxel) shows superior efficacy compared to taxane monotherapy | II | M77001; ¹¹ Slamon ¹² |

| STATEMENTS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|---|-------------------|---|
| There is conflicting evidence about the addition of carboplatin to the combination of trastuzumab with a taxane (docetaxel or paclitaxel) | II | BCIRG 007; ¹³ Robert ²¹ |
| Trastuzumab with anastrozole in women with HER2-positive hormone dependent metastatic breast cancer leads to improved progression-free survival compared with anastrozole alone | II | TAnDEM ²² |
| Phase II trials have shown evidence of safety and efficacy of trastuzumab with other single-agent systemic chemotherapies (gemcitabine, vinorelbine) | III | Burstein; ^{23,24} Jahanzeb; ²⁵ O'Shaughnessy; ²⁶ Papaldo ²⁷ |
| Phase II trials are examining the safety and efficacy of trastuzumab with other targeted therapies (gefitinib, pertuzumab) | | Moulder & Arteaga; ²⁸ Walshe ²⁹ |
| Single-agent trastuzumab | | |
| The role of first-line and subsequent line single-agent trastuzumab compared to standard systemic therapy has not been evaluated in randomised trials | | |
| Data from phase II trials support the efficacy of single-agent, first-line and subsequent line trastuzumab therapy | III | Baselga ^{30,31} |
| Continued use of trastuzumab post-progression | | |
| No randomised trials have addressed the continued use of trastuzumab alone or in combination with chemotherapy after progression of metastatic disease | | |

| STATEMENTS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|--|-------------------|---|
| Optimal dose, schedule and duration of administration | | |
| There is no evidence that a higher weekly dose (loading dose of 8 mg/kg then 4 mg/kg) is superior to a lower weekly dose (loading dose of 4 mg/kg then 2 mg/kg) of trastuzumab | II | Vogel ^{14,15} |
| Phase III trials in metastatic disease using weekly dosing schedules have continued to disease progression in the absence of unacceptable toxicity | II | M77001; ¹¹ Slamon ¹² |
| There is phase II and pharmacokinetic evidence that 3-weekly dosing (loading dose of 8 mg/kg then 6 mg/kg) gives therapeutic serum trastuzumab concentrations similar to weekly dosing once steady levels are reached and is effective and safe; however there is no direct comparison of weekly and 3-weekly dosing | III | Baselga ³¹ |
| Adverse events: | | |
| Trastuzumab with chemotherapy is associated with an increased incidence of cardiac dysfunction compared with chemotherapy alone. Long-term toxicity is unknown [^] | II | FinHer; ⁵ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |
| Trastuzumab with chemotherapy containing an anthracycline is associated with clinically relevant cardiac dysfunction in a significant proportion of patients | II | M77001; ¹¹ Slamon ¹² |

* More detailed information regarding trial results and levels of evidence are provided in the document *Trastuzumab for HER2-positive breast cancer: a systematic review* which can be accessed via the NBCC website www.nbcc.org.au

[^] For more information about adverse events associated with adjuvant trastuzumab see page 14 of this guideline.

Recommendations to individuals should be based on their risks without trastuzumab treatment, the absolute benefits, and harms of treatment, and their preference. Recommendations should also take account of any uncertainties about the long-term effects of trastuzumab treatment.

| RECOMMENDATIONS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|--|-------------------|---|
| Patients should be informed of the potential side effects of trastuzumab and any uncertainties about long-term effects | | |
| Patients receiving trastuzumab should be reviewed regularly and monitored for side effects by clinicians familiar with the drug | | |
| For patients with HER2-positive early breast cancer following surgery: | | |
| Combination with chemotherapy | | |
| Adjuvant trastuzumab should be offered with chemotherapy following surgery in patients with node-positive or node-negative tumours larger than 1 cm | II | BCIRG 006; ⁴ HERA; ⁷ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |
| Trastuzumab concurrently with an anthracycline is not recommended due to risk of cardiotoxicity | II | M77001; ¹¹ Slamon ¹² |
| Combination with radiotherapy | | |
| Trastuzumab can be offered to patients who require radiotherapy, although long-term toxicity is unknown | II | NCCTG-N9831 ¹⁸ |
| Optimal dose schedule and duration of administration | | |
| Recommended regimens based on current evidence are: Weekly: loading dose of 4 mg/kg then 2 mg/kg or 3-weekly: loading dose of 8 mg/kg then 6 mg/kg for 1 year with chemotherapy following surgery | II | HERA; ⁷ NCCTG-N9831; ⁶ NSABP-B31 ⁶ |

| RECOMMENDATIONS | LEVEL OF EVIDENCE | TRIAL AND REFERENCE |
|--|-------------------|---|
| For patients with HER2-positive locally advanced or inflammatory breast cancer: | | |
| Trastuzumab with preoperative chemotherapy can be offered to patients with locally advanced or inflammatory breast cancer | III | Hurley ²⁰ |
| For patients with HER2-positive breast cancer undergoing preoperative chemotherapy: | | |
| The use of trastuzumab following neoadjuvant chemotherapy and surgery can be offered to patients with breast cancers that are 2–5 cm in size | II | HERA ⁷ |
| For patients with HER2-positive metastatic breast cancer: | | |
| Combination with other systemic therapies | | |
| Trastuzumab with paclitaxel or docetaxel should be recommended as first-line therapy where chemotherapy is indicated | II | M77001; ¹¹ Slamon ¹² |
| Trastuzumab concurrently with an anthracycline is not recommended due to risk of cardiotoxicity | II | Slamon ¹² |
| Trastuzumab can be used with other single-agent therapies when treatment with taxanes is inappropriate; participation in relevant clinical trials should be considered | III | Burstein; ^{23,24} Jahanzeb; ²⁵ O'Shaughnessy; ²⁶ Papaldo; ²⁷ TAnDEM ²² |
| Single-agent trastuzumab | | |
| Trastuzumab can be used as single-agent therapy where combination with systemic therapy is not appropriate | II | Vogel ¹⁵ |

RECOMMENDATIONS

LEVEL OF EVIDENCE

TRIAL AND REFERENCE

Optimal dose schedule and duration of administration

Trastuzumab should be continued to disease progression in the absence of unacceptable toxicity

II

M77001;¹¹ Slamon;¹² Vogel¹⁵

Where the disease has progressed on first-line therapy containing trastuzumab, inclusion in appropriate clinical trials should be considered

Recommended regimens are:

Weekly: loading dose of 4 mg/kg then 2 mg/kg
3-weekly: loading dose of 8 mg/kg then 6 mg/kg

II

III

Vogel;¹⁵
Baselga³¹

Cardiac monitoring:

Patients with significant pre-existing cardiac dysfunction[‡] should not receive trastuzumab therapy

Patients receiving adjuvant trastuzumab should be assessed for signs of cardiac dysfunction by multi-gated acquisition (MUGA) or echocardiogram prior to treatment and reviewed clinically and by echocardiography at 3-monthly intervals during treatment

II

HERA;⁷ NCCTG-N9831;⁶
NSABP-B31⁶

Similar monitoring can be applied to patients with metastatic breast cancer if clinically appropriate

Patients who develop asymptomatic cardiac dysfunction during the course of treatment warrant more frequent monitoring, and review by a cardiologist should be considered

Consideration should be given to ceasing adjuvant trastuzumab if left ventricular ejection fraction (LVEF) is reduced by 10–15% of baseline and below normal LVEF

II

HERA;⁷
NCCTG-N9831;⁶
NSABP-B31⁶

[‡]Pre-existing cardiac dysfunction (LVEF <50) is defined as a history of documented congestive heart failure, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, and unstable arrhythmias.⁶

SUMMARY OF RESULTS

TRASTUZUMAB IN EARLY BREAST CANCER

Table 1: Details of trials in early breast cancer

| TRIAL | TRASTUZUMAB SEQUENCE | CONTROL | REGIMEN | DURATION OF TREATMENT | MEDIAN FOLLOW-UP (months) | REF |
|---------------------------|---|--|---|-----------------------|---------------------------|------|
| FinHer | concurrent with docetaxel or vinorelbine followed by FEC [†] | docetaxel or vinorelbine followed by FEC | LD: 4 mg/kg; SD: 2 mg/kg weekly | 9 weeks | 36 | 5 |
| HERA | sequential after completion of neoadjuvant or adjuvant chemotherapy [‡] | various chemotherapy | LD: 8 mg/kg; SD: 6 mg/kg 3-weekly | 1v2 years | 12 | 7, 8 |
| NSABP-B31 | after AC then concurrently with paclitaxel* | AC followed by paclitaxel | LD: 4 mg/kg; SD: 2 mg/kg weekly | 1 year | 29 | 6 |
| NCCTG-N9831 | after AC then concurrently with paclitaxel, or sequentially following paclitaxel* | AC followed by paclitaxel | LD: 4 mg/kg; SD: 2 mg/kg weekly | 1 year | 18 | 6 |
| BCIRG-006 (abstract only) | after AC with docetaxel or with docetaxel and carboplatin* | AC followed by docetaxel with A | LD: not reported; SD: not reported weekly | 1 year | 23 | 4 |
| Buzdar | after paclitaxel then concurrently with FEC (neoadjuvant)* | paclitaxel followed by FEC | SD: 2 mg/kg weekly | 24 weeks | 20 | 9 |

A= doxorubicin; C=cyclophosphamide; E= epirubicin; F= fluorouracil; LD=loading dose; RT=radiotherapy; SD=subsequent dose; *= trastuzumab concurrent with radiotherapy; [†]= prior to radiotherapy; [‡]= after radiotherapy

DISEASE-FREE SURVIVAL

All five trials in early breast cancer reported statistically significant improvements in disease-free survival in favour of trastuzumab. In the larger studies (BCIRG 006⁴ $p < 0.001$; HERA⁷ $p < 0.001$; NCCTG-N9831;⁶ NSABP-B31⁶ $p < 0.001$) the relative rate of recurrence was reduced by 40–52% among women receiving chemotherapy with trastuzumab compared to women receiving chemotherapy alone. The absolute difference in disease-free survival between women receiving trastuzumab and women receiving chemotherapy alone was between 5.5% and 12.8%. Three trials reported on distant recurrence and all showed significant improvements in women receiving trastuzumab. The relatively short follow-up must be taken into account; longer follow-up is needed to examine the effect of trastuzumab on the incidence of disease recurrence in the central nervous system.⁷

OVERALL SURVIVAL

Three trials^{6,8} in early breast cancer have reported significant improvements in overall survival in favour of trastuzumab (HERA $p = 0.001$; NCCTG-N9831; NSABP-B31 $p = 0.015$). At a median follow-up of 12–36 months overall survival was improved by 24–33%. Absolute risk reductions ranged from 0.47–6.85%, although due to the short follow-up benefits are likely to be small. A recent update of results from one trial⁸ demonstrated a statistically significant improvement in overall survival of 41% in favour of trastuzumab, although this result has been reported in abstract form only.

PREOPERATIVE TRASTUZUMAB

A number of small phase II trials have investigated preoperative trastuzumab with chemotherapy. Pathologic complete response (pCR) rates ranged from 7–47%.^{20,32-34} One randomised phase III study⁹ (42 patients) found that preoperative trastuzumab and chemotherapy was safe and effective. This study closed early due to improved interim results in women receiving trastuzumab and chemotherapy (pCR 65.2%) compared to chemotherapy alone (pCR 26.3%, $p = 0.016$). A subgroup analysis of the HERA study reported significant improvements in disease-free survival in women receiving trastuzumab with chemotherapy preoperatively. One trial found benefit to adding trastuzumab to primary systemic therapy in women with locally advanced breast cancer. At a median follow-up of 43 months, 4-year progression-free survival was 81% and overall survival was 86%.²⁰ Further research is required to establish whether the pCR rate will translate into significant disease-free and overall survival. Currently there are no data on optimal dose, long-term survival, and safety for the use of pre-operative trastuzumab.

TRASTUZUMAB IN METASTATIC BREAST CANCER

Table 2: Details of trials in metastatic breast cancer

| TRIAL | TRASTUZUMAB SEQUENCE | CONTROL | REGIMEN | DURATION OF TREATMENT | MEDIAN FOLLOW-UP (months) | REF |
|----------------------------|--|--|--|--|---------------------------|--------|
| Slamon | concurrent with doxorubicin or epirubicin plus C or paclitaxel (if received prior anthracycline) | doxorubicin or epirubicin plus C or paclitaxel (if received prior anthracycline) | LD: 4 mg/kg; SD: 2 mg/kg weekly | until disease progression | 30 | 12 |
| M77001 | concurrent with docetaxel | docetaxel | LD: 4 mg/kg; SD: 2 mg/kg weekly | until disease progression | not reported | 11 |
| Vogel | Trastuzumab as monotherapy | trial compared two doses of trastuzumab | LD: 4 mg/kg; SD: 2 mg/kg weekly vs LD: 8 mg/kg; SD: 4 mg/kg weekly | until disease progression | not reported | 14, 15 |
| Gasparini (abstract only) | concurrent with paclitaxel | paclitaxel | LD: 4 mg/kg; SD 2 mg/kg weekly | not reported | not reported | 10 |
| BCIRG 007 (abstract only) | concurrent with docetaxel | concurrent trastuzumab with docetaxel and carboplatin | LD: 4 mg/kg; SD: 2 mg/kg weekly then 6mg/kg 3-weekly | until disease progression or unacceptable toxicity | not reported | 13 |
| CALGB 9840 (abstract only) | concurrent with paclitaxel | paclitaxel | LD: 4 mg/kg; SD: 2 mg/kg weekly | until disease progression or unacceptable toxicity | not reported | 16 |

C=cyclophosphamide; LD=loading dose; SD=subsequent dose

PROGRESSION-FREE SURVIVAL

Three trials in metastatic breast cancer investigated the addition of trastuzumab to chemotherapy,¹⁰⁻¹² although data on progression-free survival are only available for two trials (M77001;¹¹ Slamon¹²). Both trials showed a statistically significant improvement in progression-free survival in favour of women receiving trastuzumab with chemotherapy (M77001: median 11.7 vs 6.1 months, $p=0.001$; Slamon: median 7.4 vs 4.6 months, $p<0.001$). Improvements were also seen in time to treatment failure, duration of response and overall response.

OVERALL SURVIVAL

Two trials in metastatic breast cancer reported data on overall survival (M77001;¹¹ Slamon¹²). Both trials showed a significant improvement in overall survival in favour of women receiving trastuzumab with chemotherapy (M77001: 31.2 vs 22.7 months, $p=0.032$; Slamon: median 25.1 vs 20.3 months, $p=0.046$). One trial¹² showed a 20% reduction in the risk of death at a median follow-up of 30 months. Improvements in survival were seen in both studies despite substantial cross-over of patients from chemotherapy alone to chemotherapy with trastuzumab after disease progression.

ADVERSE EVENTS

Cardiotoxicity

Cardiac dysfunction (CD) has been observed in patients receiving trastuzumab alone or in combination with chemotherapy. Two trials in metastatic breast cancer^{11,12} and five in early breast cancer⁵⁻⁷ have reported data related to CD. The incidence of symptomatic or asymptomatic CD was significantly higher among patients receiving trastuzumab in combination with an anthracycline (27%) compared with an anthracycline alone (8%). Serious CD was seen in 0.5–4% of women receiving adjuvant trastuzumab with a non-anthracycline.¹² Congestive heart failure associated with trastuzumab usually responded to cessation of therapy and management. Longer follow-up is needed to determine possible long-term cardiotoxicity associated with trastuzumab.

Other adverse events

Two trials^{11,12} in metastatic breast cancer have reported higher rates of infection, leukopenia, anaemia and neutropenia in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone, although fewer patients receiving trastuzumab discontinued treatment due to adverse events.¹¹ In one trial, 10% of women with metastatic breast cancer receiving trastuzumab in combination with chemotherapy developed isolated central nervous system (CNS) metastases as first site of tumour progression.³⁵ It is unclear whether CNS metastases are associated with the biology of HER2-positive breast cancer or develop as a result of trastuzumab treatment. A low incidence of transfusion-related reactions associated with trastuzumab treatment has also been reported.

Trials in early breast cancer^{5,6} have reported little difference in adverse effects other than CD. The follow-up periods reported were insufficient for information on longer term side effects to be ascertained.

CARDIAC MONITORING

Eligibility criteria for entry into the most recent trials included in this guideline required patients to have a (LVEF) >50%. Patients were screened prior to commencement of trastuzumab and at 3-monthly intervals for the duration of treatment.⁶ Initial screening included a cardiac questionnaire, physical examination, 12-lead electrocardiogram and an assessment of LVEF by echocardiography.⁷ Decline in LVEF was the primary indicator of CD and was assessed using either multi-gated acquisition (MUGA) or echocardiogram. Degree of symptoms was usually classified using the New York Heart Association (NYHA) classification or the National Cancer Institute Common Toxicity Criteria.

QUALITY OF LIFE

Formal analyses of quality of life for patients receiving trastuzumab are limited. One study³⁶ reported a statistically significant improvement in quality of life in women with metastatic disease receiving chemotherapy and trastuzumab compared with chemotherapy alone (51% vs 36%). Women receiving trastuzumab also reported improvements in fatigue and physical and role functioning (not significant). Further research is required to determine the short- and long-term effects of trastuzumab on quality of life.

ASSESSMENT OF HER2 STATUS

Assessment of HER2 status should be performed on samples obtained by core or surgical biopsy. Trials used immunohistochemistry (IHC) to detect over-expression of the HER2 protein, or in-situ hybridisation (ISH) to detect the amplified gene. ISH includes fluorescence in-situ hybridisation (FISH) and chromogenic in situ hybridisation (CISH). Trials in metastatic breast cancer defined HER2-positive as an IHC score of 2+ or 3+ or as FISH-positive. A reanalysis of randomised trial data found that patients with IHC scores of 3+ were more likely than those with scores of 2+ to respond to trastuzumab. Retesting of the tumours by FISH also found that patients who did not respond to trastuzumab were more likely to be FISH-negative. FISH-positive patients had higher overall response rates and longer survival compared with FISH-negative patients.³⁷ Trials in early breast cancer defined HER2-positive as an IHC score of 3+, FISH-positive or CISH-positive.

In Australia, eligibility for trastuzumab by patients with metastatic breast cancer is dependent on an IHC score of 3+ or a positive ISH test (FISH or CISH). For patients with an IHC score of 2+, subsequent confirmation by ISH is required. Eligibility for trastuzumab by patients with early breast cancer is dependent on a positive ISH test.

STRENGTHS AND WEAKNESSES OF THE AVAILABLE EVIDENCE

The randomised trials discussed in this guideline are large, well designed, and well conducted. Information about long-term results on overall survival and adverse effects for both metastatic breast cancer and early breast cancer is not yet available. These clinical practice recommendations developed by the NBCC will be reviewed as additional significant evidence becomes available and revised as required.

UNANSWERED QUESTIONS

Important unanswered questions about the use of trastuzumab in metastatic breast cancer and adjuvant therapy are outlined below; some of these should be addressed in ongoing trials:

- optimal duration of adjuvant trastuzumab with chemotherapy
- optimal sequence/timing of adjuvant trastuzumab with chemotherapy
- continued use of trastuzumab post-progression in patients with metastatic breast cancer
- use of trastuzumab with other systemic and targeted therapies as adjuvant therapy and in metastatic breast cancer
- use of trastuzumab as single-agent therapy, as adjuvant therapy, and in metastatic breast cancer
- use of trastuzumab in patients with node-negative, HER2-positive tumours smaller than 1 cm
- use of trastuzumab in locally advanced and inflammatory breast cancer
- use of trastuzumab in older women
- long-term adverse effects of trastuzumab on cardiac function and the natural history of trastuzumab-induced cardiac dysfunction
- effect of trastuzumab on the incidence of disease recurrence in the central nervous system
- long-term benefits and adverse effects of adjuvant trastuzumab
- quality of life issues associated with the use of trastuzumab
- use of trastuzumab in pregnancy, and impact on fertility and contraception.

ONGOING TRIALS

A number of ongoing phase III trials are investigating the use of trastuzumab in HER2-positive breast cancer:

- five ongoing trials investigating the use of trastuzumab in early breast cancer (BIG-01-01 (HERA);³⁸ NSABP-B31;³⁹ NCCTG-N9831;¹⁹ UCLA-0102006 (BCIRG 006);⁴⁰ FRE-FNCLCC-PACS-04/0005⁴¹)
- three ongoing trials investigating the use of trastuzumab as preoperative therapy (CLB 49808;⁴² GBG-GEPARQUATTRO;⁴³ ID99-146⁴⁴)
- four ongoing trials investigating the use of trastuzumab in metastatic breast cancer (SWS-SAKK-22/99;⁴⁵ EGF 104383;⁴⁶ UCLA-0109024 (BCIRG-007)⁴⁷)
- three ongoing trials investigating the continued use of trastuzumab post-progression (SWOG SO347;⁴⁸ GBG26;⁴⁹ EGF 104900⁵⁰).

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This guideline was developed by a multidisciplinary working group convened by the National Breast Cancer Centre

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Systematic review

The NBCC gratefully acknowledges the work of Ms Davina Gheri and Ms Sharon Parker at the National Health and Medical Research Council Clinical Trials Centre, Sydney in developing the systematic review *Trastuzumab for HER2-positive breast cancer: a systematic review* (2006), which informed the development of this guideline.

Pharmaceutical Benefits Scheme listing for trastuzumab (as of November 2006). For updates after this date go to <http://www.medicareaustralia.gov.au/providers>

Herceptin® (Trastuzumab) is currently subsidised for the treatment of HER2-positive patients with metastatic breast cancer:

- in combination with taxanes for patients who have not received chemotherapy for metastatic disease
- as monotherapy for the treatment of those patients who have received one or more chemotherapy regimen(s) for metastatic disease.

Herceptin® (Trastuzumab) is currently subsidised for the treatment of HER2-positive patients with early breast cancer:

- concurrently with chemotherapy following surgery; restrictions apply, see website for further information.

NOTES

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Full details of trial results are provided in the document *Trastuzumab for HER2-positive breast cancer: a systematic review* which can be accessed via the NBCC website at www.nbcc.org.au

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