

REGIONAL DRUG AND THERAPEUTICS CENTRE

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RAPID APPRAISAL

Name of Trial: Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer.

Reference: Romond HE, Perez EA, Bryant J, et al. N Engl J Med:2005;353:1673-84

Question: What is the efficacy and safety of trastuzumab as adjuvant therapy in women with surgically removed HER2-positive early-stage breast cancer?

Summary: This interim analysis showed that the addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide produced a significantly improved benefit in terms of disease-free-survival of 11.8% at three years and 18.2% at four years. Furthermore, the addition of trastuzumab reduced the mortality rate by 2.5% at three years and by 4.8% at four years. This benefit was apparently independent of the patient's age, nodal status, hormone receptor status or tumour grade. A corresponding benefit in overall survival was not seen in the additionally published HERA study. Interpretation of the results must take into account the very short follow-up period (median 2 years). There are concerns regarding the safety of trastuzumab with the associated increased risk of cardiotoxicity, which in the future, published longer term data may help to clarify.

Did the study ask a clearly focussed question?

Yes - This joint analysis of 2 separate studies was designed to assess the efficacy and safety of trastuzumab as adjuvant therapy in women with surgically removed HER2-positive early-stage breast cancer.¹ The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every three weeks with the same regimen plus 52 weeks of trastuzumab beginning with the first dose of paclitaxel. The North Central Cancer Treatment Group (NCCTG) trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel, the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel, and the same regimen followed by 52 weeks of trastuzumab after paclitaxel. The joint analysis compared the combined control groups with the combined concomitant trastuzumab groups.

The primary endpoint was disease-free-survival, defined as time from randomisation to recurrence of cancer, contralateral breast cancer, development of a second primary cancer or death before recurrence. Secondary endpoints included overall survival, time to distant recurrence, death from breast cancer, contralateral breast cancer, and other second primary cancers.

Was the study design appropriate?

Yes - Both studies were large prospective, randomised, control trials. Eligible patients had HER2 overexpression or amplification of the HER2 gene on fluorescence in situ hybridization. Initially, both trials required patients to have histologically proven, node positive disease. As of 2nd May 2003, patients with high risk node negative disease were eligible for trial N9831. The control groups, as well as the concomitant trastuzumab groups of the two trials, differed in terms of the scheduling of paclitaxel treatment and some aspects of hormonal therapy and radiotherapy, but were otherwise identical. For this reason a joint analysis plan to combine the data from both trials for comparison was approved by the primary sponsor, the National Cancer Institute (NCI), and the Food and Drug Administration (FDA).

One patient group within trial N9831 was appropriately excluded from this joint analysis because the protocol required administration of trastuzumab after the completion of chemotherapy. One interim analysis was planned after the occurrence of 355 primary-endpoint events and a definitive analysis was scheduled after 710 events. Data was reviewed by an Independent Data Monitoring Committee (IDMC) and consideration was to be given to early reporting if disease-free survival differed at the nominal 0.0001 level.²

Cardiac toxicity has been reported in women who have received the drug as a single agent.^{3,4} In both trials left ventricular ejection fraction (LVEF) was assessed before entry, after the completion of doxorubicin and cyclophosphamide therapy, and 6, 9 and 18 months after randomisation. Initiation of trastuzumab required an LVEF after doxorubicin and cyclophosphamide therapy that met or exceeded the lower limit of normal and a decrease of less than 16% from baseline. The 6 and 9 months assessments were used to determine whether trastuzumab treatment should be continued in patients without cardiac symptoms.

Genentech provided trastuzumab and partial funding support for both trials but did not participate in the study design or the collection of data. The joint analysis was developed and analysed by the NCCTG and NSABP.

Were participants appropriately allocated to intervention and control groups?

Yes - In trial B-31, treatment assignments were balanced according to nodal status, planned hormonal therapy, type of surgery, intended radiotherapy and institution using a biased-coin minimisation algorithm⁵ Trial N9831 used a dynamic allocation procedure which balanced the distribution of nodal status and hormone receptor status between groups.⁶

Were participants, staff and study personnel 'blind' to participants study group?

Can't tell – No reference to blinding of patients, staff or investigators is apparent in the published article.

Were all of the participants who entered into the trial accounted for at its conclusion?

Yes - A flow diagram accounts for all randomised patients up to entry in the intention-to-treat analysis. In the combined trials, 31 of the 1,843 patients in the control group declined therapy, as did 9 of the 1,833 women randomly assigned to trastuzumab therapy. The intention to treat analysis included all patients who declined protocol therapy for whom follow-up was available.

Were the participants in all groups followed up and data collected in the same way?

Yes – In trial B-31 of the 2,043 patients enrolled 1736 had at least one follow-up evaluation (end point evaluation was not required for 6 months after randomisation). In trial N9831 of the 1,633 patients enrolled, 1,615 had follow up evaluations. However at the time of analysis follow-up data was only available for 1,679 patients in the combined control arms and 1,672

patients in the combined trastuzumab arms. The timing and methods of the follow-up procedure are not stipulated.

Was the study large enough?

Yes – Power calculations indicated that 710 primary-endpoint events were needed to detect a 25% reduction in the event rate with a statistical power of 90%. The first interim analysis was to take place after 355 events had been reported. Subsequent interim analyses were scheduled to take place semi-annually.

A joint, interim analysis was performed after 394 primary-endpoint events had been reported based on data from 3,351 patients. The IDMC of each trial recommended closing enrolment and early release of the results.

How are the results presented and what is the main result?

The analysis was performed after 394 events had been reported. Of these 133 were in the trastuzumab group and 261 in the control group, This was at a median follow up of 2.0 years (2.4 years in trial B-31 and 1.5 years in trial N9831). Kaplan-Meier curves of disease-free survival and overall survival are presented and the unadjusted hazard ratios (HR) (with 95% confidence intervals (CI) and p values) were computed and compared according to length of follow up.

The HR for the primary endpoint, disease-free-survival was 0.48 (p<0.0001). The percentage of patients alive and disease-free at three years was 75.4% in the control group and 87.1% in the trastuzumab group. This corresponds to an absolute difference in disease-free-survival of 11.8% (95% CI, 8.1% -15.4%). At four years, the respective figures were 67.1% and 85.3% and an absolute difference of 18.2% (12.7% - 23.7%). This difference crossed the early stopping boundary. The HR (0.67) for overall survival was statistically significant (p=0.015) between the two groups with 62 deaths in the trastuzumab group as compared with 92 deaths in the control group. The absolute survival rate at three years was 94.3% in the trastuzumab group and 91.7% in the control group (absolute difference, 2.5% (0.1% - 5.0%)). At four years the respective figures were 86.6% and 91.4% (absolute difference 4.8% (0.6% - 9.0%).

Distant metastases were reported in 193 patients in the control group and 96 in the trastuzumab group. The HR for a first distant recurrence was 0.47 in the trastuzumab group compared with the control group (p<0.0001). At three years 90.4% of women were free of distant recurrence, as compared with 81.5% of women in the control group with an absolute difference 8.8% (5.5% - 12.1%). The respective rates at four years were 89.7% and 73.7% (absolute difference of 15.9% (11.1% - 20.8%).

How precise are the results?

Both studies included in this joint analysis were large multi-centred randomised control trials which were well-designed and conducted. Baseline characteristics were similar for both groups. All participants were accounted for and followed up. The interim analysis was conducted strictly according to protocol. The use of an early stopping boundary was stipulated in the study protocol and applied appropriately. Because improvements in disease-free-survival crossed the sequential boundary at three and four years, for trastuzumab compared with control, the recommendation of the IDMC to publish the results at interim analysis appears justified.

The HR for the primary endpoint disease-free-survival was highly significant ($p < 0.0001$). The 95% confidence interval is narrow and does not approach the line of no effect (0.39 - 0.59). The HR for overall survival was also statistically significant ($p = 0.015$). However, the confidence intervals are wide (95% CI 0.48 - 0.93).

However, due to these results, the trial was stopped after the first analysis. This modification, although clearly appropriate, will impair subsequent analyses and could lead to an underestimation of the overall benefit of trastuzumab therapy.

A Cox model was fitted to disease free survival to adjust for additional characteristics (treatment assignment, nodal status, pathological tumour size, hormone-receptor status, age, tumour grade, tumour histology, and trial). Adjustment for these factors minimally affected the results (HR for disease-free-survival 0.46 (95% CI 0.37 - 0.56, $p < 0.001$). There was no evidence that the benefit of trastuzumab differed significantly between the two trials ($p = 0.38$).

How safe were the regimens?

In trial B-31, of those patients who met the requirements for the initiation of trastuzumab therapy the cumulative incidence of New York Heart Association (NYHA) class III or IV congestive heart failure (CHF) or death from cardiac causes at three years was 0.8% in the control group (4 patients had CHF, and 1 died from cardiac causes) compared to 4.1% in the trastuzumab group (31 patients had CHF). In trial N9831, the cumulative incidence of NYHA class III or IV CHF or death from cardiac causes at three years was 0% in the control group and 2.9% in the trastuzumab group (20 patients had CHF, 1 of whom died of cardiomyopathy). It should be noted that some episodes of severe heart failure may have been avoided because of the use of LVEF monitoring in asymptomatic patients.

Of the 1159 patients with an adequate LVEF after doxorubicin and cyclophosphamide treatment

that began trastuzumab treatment and have completed therapy, 364 (31.4%) discontinued treatment before 52 weeks. Reasons for discontinuation were recurrence in the case of 22 patients (1.9%), a confirmed asymptomatic decline in LVEF in 164 (14.2%), symptoms of CHF and other adverse cardiac effects in 54 (4.7%), non cardiac adverse effect in 27 (2.3%), patient-initiated discontinuation in 70 (6.0), and other reasons in 27 (2.3%).

There was no significant difference in the incidence of any common toxicity criteria between the two groups, except for a higher incidence of left ventricular dysfunction in the trastuzumab group. However, a low number of cases of interstitial pneumonitis were reported that appeared in some cases to be related to trastuzumab therapy. In the B-31 trial, 4 patients had interstitial pneumonitis, one of whom died. In the N9831 trial, 5 patients had grade 3+ pneumonitis or pulmonary infiltrates, one of whom died.

Can the results be applied to the local population?

The study population comprised of women who had surgically removed early-stage HER2-positive breast cancer and had completed a regimen of doxorubicin and cyclophosphamide. Both lymph node-positive and lymph node-negative patients were eligible for entry to the trial.

However, exclusion of certain patient groups from the trial precludes the results from being applicable to all women with HER2 positive breast cancer. Women with small-node negative invasive tumours and those with cardiac risk factors and an LVEF below the lower limit of normal were excluded. Therefore, it is unclear as to how the results may translate to lower risk patients (node negative tumours of less than 1 cm), those with cardiac dysfunction following chemotherapy, or those patients not given chemotherapy.

In 2000, the incidence of breast cancer in the UK was 57 per 100,000 population. Approximately 80% of these are likely to present with early-stage disease. Of these only 20-30% will be HER2-positive and therefore eligible candidates for adjuvant treatment with trastuzumab.⁷

Trastuzumab is not currently licensed for the treatment of early breast cancer.⁸

What is the efficacy and safety of trastuzumab as adjuvant therapy in women with surgically removed HER2-positive early-stage breast cancer?

This study showed that the addition of trastuzumab to paclitaxel after a regimen of doxorubicin and cyclophosphamide produces a significantly improved benefit in terms of disease-

free-survival of 11.8% at three years and 18.2% at four years. Furthermore, the addition of trastuzumab reduced the mortality rate by 2.5% at three years and by 4.8% at four years. This benefit was apparently independent of the patient's age, nodal status, hormone receptor status or tumour grade. A corresponding benefit in overall survival was not observed in the additionally published HERA study.⁹

Despite systemic control of the disease an increase in the frequency of brain metastases has been reported among patients with metastatic breast cancer treated with trastuzumab.^{10,11} In this trial, isolated brain metastases as first events were more common in the trastuzumab group than in the control group (21 vs. 11 in trial B 31, and 12 vs. 4 in trial N9831). Patients in trial B31 were followed for additional recurrences beyond the first distant event, and brain metastases as a first or subsequent event were diagnosed in 28 patients in the trastuzumab group compared with 35 in the control group (HR 0.79, p=0.35). The imbalance in brain metastases as first events was attributed to earlier failures at other distant sites among patients in the control group.

A further concern regarding the safety of trastuzumab is the associated increased risk of cardiotoxicity.^{3,4} The cumulative three-year incidence of congestive heart failure increased by about 3% with the addition of trastuzumab. Additional follow-up will be needed to determine the long-term cardiotoxicity of trastuzumab.

The relatively low overall incidence of cardiac side effects observed in this trial may be related to the fact that patients with insufficient cardiac function after chemotherapy had been excluded.

Therefore appropriate selection and careful cardiac monitoring of patients receiving trastuzumab is essential. Trastuzumab did not increase the overall frequency of non cardiac adverse effects associated with the chemotherapy regimens. However, the incidence of pneumonitis (two of which were fatal); in patients receiving trastuzumab is a cause for concern.

Because trastuzumab offers no benefit to patients whose tumours do not overexpress HER2 careful testing must be done to establish those candidates eligible for treatment. A recent study showed that 18% of community-based assays used to confirm the HER2-positive eligibility of participants in the B-31 trial could not be confirmed by a central testing facility.¹² Therefore testing would need to be done at high volume laboratories with strict quality control procedures in order to reduce the number of false positive tests.

The results of the trial suggest that of adjuvant trastuzumab combined with paclitaxel therapy could be considered as part of optimal systemic therapy for women with HER2-positive early-stage breast cancer on completion of locoregional surgery and chemotherapy (doxorubicin and cyclophosphamide), who fulfil the eligibility criteria of the study. However, the long-term efficacy and safety of trastuzumab has yet to be established and as yet is not licensed for this indication.

Trastuzumab costs in the region of £22,400 per year and therefore poses potentially significant financial implications due to drug, service and testing costs.

REFERENCES

1. Romond HE, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer *N Engl J Med*:2005;353:1673-84
2. Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika*: 1983;70:659-63
3. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2 overexpressing metastatic breast cancer. *J Clin Oncol*. 2002;20:719-26
4. Baselga J, Carbonell X, Castaneda-Soto NJ, et al. Phase II study of efficacy, safety, and pharmacokinetics of trastuzumab monotherapy administered on a 3-weekly schedule. *J Clin Oncol*. 2005; 23:2162-715
5. White SJ, Freedman LS. Allocation of patients to treatment groups in a controlled clinical study. *Br J Cancer*. 1978; 37:849-57
6. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics*. 1975; 31:103-15
7. UK Medicines Information/ National Prescribing Centre Prescribing Outlook September 2005. Pipeline Drugs – Trastuzumab inj; page 15.
8. Herceptin® Summary of Product Characteristics; Roche Products Limited. Accessed www.emc.medicines.org 31/10/2005
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2 positive breast cancer *N Engl J Med*: 2005;353:1659-72
10. Bendell JC, Domcheck SM, Burtsein HJ, et al. Central nervous system metastases in women who received trastuzumab-based therapy for metastatic breast carcinoma. *Cancer*. 2003; 97:2972-7
11. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. *Br J Cancer*. 2004; 91:639-43
12. Paik S, Bryant J, Tan-Chiu E, et al. Real-world performance of HER2 testing--National Surgical Adjuvant Breast and Bowel Project experience. *J Natl Cancer Inst*. 2002;94:852-4.

This document should be read alongside Rapid Appraisal No. 8

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