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RAPID APPRAISAL

Name of Trial: Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer

References: Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. N Engl J Med: 2005;353:1659-72

Question: What is the efficacy and safety of adjuvant trastuzumab in HER2- positive patients with early-stage breast cancer?

Summary: This interim analysis showed that trastuzumab when given after completion of chemotherapy to women with early stage HER2-positive breast cancer produces a significantly improved benefit in terms of disease-free-survival of 8.4% at two years. Benefit was independent of the patient's age, nodal status, hormone receptor status and the type of adjuvant chemotherapy the women had received. Overall survival, however was not statistically different between the two groups with 29 deaths in the trastuzumab group and 37 in the observation group (P=0.26). In the published B31/N9381 trial, however, the addition of trastuzumab reduced the mortality rate by 2.5% at three years and by 4.8% at four years. Interpretation of the results must take into account the very short follow-up period (median 1 year). There is concern that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. A further concern regarding the safety of trastuzumab is the associated increased risk of cardiotoxicity.

Did the study ask a clearly focussed question?

Yes - This study was designed to assess the efficacy and safety of trastuzumab as adjuvant therapy in women with HER2-positive early-stage invasive breast cancer, who had completed locoregional therapy and at least four cycles of chemotherapy.¹ Participants were randomly assigned to one year of treatment with trastuzumab, two years of treatment, or to be observed without receiving trastuzumab. The treatment group received a one or two year course of trastuzumab administered intravenously. The first dose was 8mg/kg body weight and subsequent doses of 6mg/kg were given every three weeks. The primary endpoint was disease free survival, defined as time from randomisation to recurrence of breast cancer at any site, development of a second cancer, or death from any cause. Secondary endpoints included cardiac safety, overall survival, site of first disease-free-survival event, and time to distant recurrence.

Was the study design appropriate?

Yes - The Herceptin Adjuvant (HERA) trial was a prospective, randomised, open-label, controlled trial. Eligible patients had histologically confirmed, completely excised invasive breast cancer with HER2 overexpression or amplification confirmed by a central trial laboratory before randomisation. The study allowed for the use of a wide range of chemotherapy regimens, and both lymph node-positive and lymph node-negative patients were eligible for entry into the trial. One interim efficacy analysis was planned after the occurrence of 475 disease-free-survival 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 After a median follow up of one year, the IDMC released detailed information for the groups assigned to one year of trastuzumab treatment or observation. These groups are the focus of this study; evaluation of the group assigned to two years treatment is ongoing. Cardiac toxicity has been reported in women who received the drug as a single agent.^{3,4}

Consequently, careful cardiac monitoring and stopping rules were specified for cardiotoxicity such that only patients who, after completion of all chemotherapy and radiotherapy, had normal left ventricular ejection fraction (LVEF, $\geq 55\%$) were eligible to take part in the study. If there was an absolute difference of $>4\%$ in the incidence of severe congestive heart failure (CHF) or cardiac death between the two groups, the trial would also be stopped or modified. Three prespecified cardiac analyses were performed after 300, 600 and 900 patients had been enrolled and treated for at least six months. Financial support and the drug were provided by Roche.

Were participants appropriately allocated to intervention and control groups?

Yes – A total of 5,081 patients were randomly assigned to one of three groups within seven weeks from day one of the last chemotherapy cycle, or six weeks from the end of radiotherapy or definitive surgery. 1694 were assigned to two years of trastuzumab, 1694 assigned to one year of trastuzumab, and 1693 assigned to observation. A minimisation procedure according to the methods of Pocock and Simon was used,⁵ with stratification according to region of the world, age, nodal status, type of chemotherapy and hormone-receptor status together with intention to use endocrine therapy. There were major eligibility violations in 11 patients (8 patients in the trastuzumab group and 3 patients in the observation group). In addition, 39 patients in the trastuzumab group and 52 patients in the observation group had node-negative tumours 1cm in diameter or less. All were included in the intention-to-treat efficacy analysis. For the planned interim analysis the baseline characteristics of the two groups were well balanced with the exception of those not having received adjuvant endocrine therapy. However, the difference between the two groups does not influence the results. The median time between diagnosis and initiation of trastuzumab was 8.4 months.

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

NO - Both participant and investigator were aware of which treatment the participant was receiving.

However, the study was conducted under the auspices of the Breast International Group (BIG) and involved the collaboration of 17 BIG groups, 9 other cooperative groups and 91 independent centres. All of which, along with the pharmaceutical sponsor were represented on the steering committee who designed the trial. Access to the database was restricted to data managers of the Breast European Adjuvant Study Team data centre and independent

statisticians. The company had no access to the database or interim analyses. The analyses were presented by the independent statisticians to the independent monitoring committee without disclosure to the data centre, investigators or sponsor. The steering committee was responsible for the decision to publish and for the content of the manuscript.

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. Trastuzumab was stopped before completion of the planned one-year treatment in 143 patients (8.5%) for reasons other than relapse. Reasons included adverse event (5.5%), patient refusal (2.5%) and other reasons (0.5%). All were included in the intention-to-treat and safety analyses. Twenty patients assigned to one year of trastuzumab did not receive treatment, and three patients assigned to observation received trastuzumab. These patients were included in the alternative group for safety analysis (1677 trastuzumab and 1710 observation patients).

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

YES – All patients were followed-up and all adhered to the same clearly defined schedule of follow-up visits. This required the recording of symptoms, side effects, and findings on clinical examination every three months for the first two years, with haematological and chemistry studies every six months. These assessments are scheduled to occur annually for years 3 to 10, with annual chest radiography to year 5 and annual mammography to year 10.

Was the study large enough?

YES - Power calculations indicated that enrolment of 4482 patients would be needed to detect a 23% relative reduction in the risk of a disease-free-survival event with 80% power, at a two sided significance level of 2.5% for each comparison (two years of trastuzumab vs. observation, and one year of trastuzumab vs. observation). A total of 951 disease-free-survival events are required for the final analysis (expected median follow-up of two years) and 475 for the interim efficacy analysis (median follow-up of one year).

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

The IDMC recommended release of the results because improvements in disease free survival were highly significant, crossing the sequential boundary for both one and two years of trastuzumab, compared to observation.

The analysis was performed when 347 events (recurrence of breast cancer at any site, contralateral breast cancer, second non-breast malignant disease, or death) had been observed: 127 events in the trastuzumab group and 220 in the observation group. This was at median follow-up of one year (range, 0 to 36 months). Kaplan-Meier curves were presented and the hazard ratios (HR) (with 95% confidence intervals (CI) and p values) were obtained from an unadjusted Cox proportional hazard regression model. The unadjusted HR for the risk of an event in patients assigned to receive trastuzumab for one year, as compared with those assigned observation, was 0.54 ($p<0.0001$). This corresponded to an absolute benefit in disease-free-survival of 8.4% at two years. The majority of events for both groups (67%) were distant metastases. The HR for time to a distant recurrence for the trastuzumab group compared to observation was 0.49. The HR (0.76) for overall survival was not statistically different ($p=0.26$) in the two groups with 29 deaths in the trastuzumab group and 37 in the observation group. There was no evidence of substantial heterogeneity in the relative treatment effect among the subgroups.

How precise are the results?

This was a large phase III, multi-centred randomised control trial which was well-designed and conducted. Baseline characteristics were similar for both groups. All participants were accounted for and followed up regularly. The interim efficacy 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 for both one and two years of trastuzumab compared with observation, the recommendation of the IDMC to publish the results at interim analysis appears justified.

The HR for the primary endpoint was highly significant ($p<0.0001$). The 95% confidence interval is narrow and does not approach the line of no effect (0.43-0.67). The HR for time to distant recurrence was also highly significant ($p<0.0001$) and also did not approach the line of no effect (95% CI 0.38-0.63). Overall survival between the two groups was not statistically significant ($p=0.26$) with wide confidence intervals crossing the line of no effect (0.47-1.23). The published analysis only includes the observation and one year treatment groups. Assessment of

the group assigned to two years of treatment with trastuzumab is ongoing. After the trial stopped, following the first interim analysis, trastuzumab was offered to all patients in the observation group. This modification, although clearly appropriate, will impair subsequent analyses and could lead to an underestimation of the overall benefit of trastuzumab therapy.

How safe were the regimens?

There was a higher incidence of grade 3 or 4 adverse events (7.9% vs. 4.4%, $p<0.001$) and serious adverse events (7.0% vs. 4.7%, $p=0.007$) in the trastuzumab group. 8.5% of patients allocated to receive trastuzumab stopped before completion of treatment for reasons other than relapse. There were six fatal adverse events in the trastuzumab group and three in the observation group. The incidence of severe CHF was higher in the trastuzumab group compared to that in the observation group (0.54% vs. 0.0%, $p=0.002$). Symptomatic CHF, including severe CHF was also higher in the trastuzumab group (1.73% vs. 0.06%, respectively, $p<0.001$). A decreased LVEF was noted in at least one assessment among 7.08% of patients in the trastuzumab group compared to 2.21% ($p<0.001$) among the observation group. However, the short follow-up period for this interim analysis meant that any long-term potentially cardiotoxic effects of trastuzumab could not be assessed. Patients in the study will continue to be monitored for any potential adverse effects for up to 10 years.

Can the results be applied to the local population?

The study population was comprised of women with HER2-positive early-stage invasive breast cancer who had completed locoregional therapy and neoadjuvant or adjuvant chemotherapy. The study allowed for a wide range of chemotherapy regimens in addition to radiation or hormonal (tamoxifen or aromatase inhibitors) therapy if appropriate. 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/or those with cardiac risk factors and/or an LVEF of less than 55% were excluded. Therefore, it is unclear as to how the results may translate to lower risk patients (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.⁶ Trastuzumab is not currently licensed for the treatment of early breast cancer.⁷

What is the efficacy and safety of adjuvant trastuzumab in HER2- positive patients with early-stage breast cancer?

This study showed that trastuzumab when given after completion of chemotherapy to women with early stage HER2-positive breast cancer produces a significantly improved benefit in terms of disease-free-survival of 8.4% at two years. This benefit was independent of the patient's age, nodal status, hormone receptor status and the type of adjuvant chemotherapy the women had received. However, overall survival was not statistically different between the two groups with 29 deaths in the trastuzumab group and 37 in the observation group (P=0.26). Interpretation of the results must take into account the very short follow-up period (median 1 year). It is conceivable that a longer follow-up may have shown an improvement in overall survival. In the other trastuzumab trial⁸, published in the same journal, the mortality rate was reduced; by 2.5% at three years and by 4.8% at four years. Approximately two thirds of the reported first events in this trial were distant metastases. There is one concern, that longer follow-up may show that trastuzumab is not effective in reducing the incidence of disease recurrence in the central nervous system. 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.^{9, 10} A further concern regarding the safety of trastuzumab is the associated increased risk of

cardiotoxicity.^{3,4} This study provides only preliminary information on the cardiac toxicity. Serious life-threatening (and in rare cases, fatal) cardiac events, most commonly CHF occurred approximately 3-4% more often in those patients receiving trastuzumab and chemotherapy than in those receiving chemotherapy alone. 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. Appropriate selection and careful cardiac monitoring of patients receiving trastuzumab is essential.

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 NSABP B-31 trial could not be confirmed by a central testing facility.¹¹ 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 1 year of adjuvant trastuzumab 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 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. 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
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; 23:2162-71
5. Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics. 1975; 31:103-15
6. UK Medicines Information/ National Prescribing Centre Prescribing Outlook September 2005. Pipeline Drugs – Trastuzumab inj; page 15.
7. Herceptin® Summary of Product Characteristics; Roche Products Limited. Accessed www.emc.medicines.org 31/10/2005
8. 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
9. 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
10. 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
11. 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.

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