2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial

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Summary

Background **Trastuzumab—a humanised monoclonal antibody against HER2—has been shown to improve disease-free survival after chemotherapy in women with HER2-positive early breast cancer. We investigated the drug's effect on overall survival after a median follow-up of 2 years in the Herceptin Adjuvant (HERA) study.**

Methods **HERA is an international multicentre randomised trial that compared 1 or 2 years of trastuzumab treatment with observation alone after standard neoadjuvant or adjuvant chemotherapy in women with HER2-positive node positive or high-risk node negative breast cancer. 5102 women participated in the trial; we analysed data from 1703 women who had been randomised for treatment with trastuzumab for 1 year and 1698 women from the control group, with median follow-up of 23·5 months (range 0–48 months). The primary endpoint of the trial was disease-free survival. Here, we assess overall survival, a secondary endpoint. Analyses were done on an intent-to-treat basis. This trial is registered with the European Clinical Trials Database, number 2005–002385–11.**

Findings **97 (5·7%) patients randomised to observation alone and 58 (3·4%) patients randomised to 1 year of treatment with trastuzumab were lost to follow-up. 172 women stopped trastuzumab prematurely. 59 deaths were reported for trastuzumab and 90 in the control group. The unadjusted hazard ratio (HR) for the risk of death with trastuzumab compared with observation alone was 0·66 (95% CI 0·47–0·91; p=0·0115). 218 disease-free survival events were reported with trastuzumab compared with 321 in the control group. The unadjusted HR for the risk of an event with trastuzumab compared with observation alone was 0·64 (0·54–0·76; p<0·0001).**

Interpretation **Our results show that 1 year of treatment with trastuzumab after adjuvant chemotherapy has a significant overall survival benefit after a median follow-up of 2 years. The emergence of this benefit after only 2 years reinforces the importance of trastuzumab in the treatment of women with HER2-positive early breast cancer.**

Introduction

Trastuzumab (Herceptin; Roche, Basel, Switzerland) is a humanised monoclonal antibody that is targeted against the extracellular domain of the HER2 transmembrane growth factor receptor.[1] Amplification of the HER2 gene and overexpression of the receptor occurs in around 15–25% of women with early breast cancer, and is associated with an aggressive disease course.[2,3] Trastuzumab has been shown to be of overall survival benefit to women with HER2-positive metastatic breast cancer administered alone[4,5] or in combination with chemotherapy.[6,7]

The Herceptin Adjuvant (HERA) trial (Breast International Group 0101) is one of several large trials designed to test the efficacy of trastuzumab in the adjuvant (ie, postsurgery) treatment of women with HER2-positive early breast cancer. Results of a first planned interim analysis with a median 1-year follow-up showed that trastuzumab given every 3 weeks for 1 year after adjuvant or neoadjuvant (ie, presurgery) chemotherapy achieved a significant improvement in disease-free survival compared with women treated with adjuvant chemotherapy alone, with a hazard ratio (HR) of 0·54.[8]

The combined analysis of two similar North American trials (North Central Cancer Treatment Group Trial N9831 and National Surgical Adjuvant Breast and Bowel Project B-31) has also shown a significant improvement in disease-free survival for trastuzumab given concurrently with four courses of paclitaxel either every week or every 3 weeks after a combination of doxorubicin and cyclophosphamide and continued for 1 year compared with the same chemotherapy schedule alone.[9] A fourth adjuvant trastuzumab trial, known as BCIRG 006, has also shown much the same disease-free survival benefit when trastuzumab is given either with docetaxel after doxorubicin and cyclophosphamide or with docetaxel and carboplatin.[10] Finally, a fifth, much smaller, trial has also shown an improvement in disease-free survival after only 9 weeks of trastuzumab given at the start of treatment concurrently with adjuvant chemotherapy.[11]

The magnitude of the benefit, with a reduction in the early risk of recurrence of around 50% in all these trials, has led to the widespread use of trastuzumab as adjuvant therapy. However, this use has been criticised by some

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because the findings arise from interim analyses, follow-up is short, and significant overall survival benefit has not been shown in any stand alone trial.[12] Our aim is to report an analysis of overall survival, together with an updated assessment of disease-free survival, in the HERA trial with a median 2-year follow-up.

Methods

Patients

The study design, eligibility criteria, treatment schedules, monitoring, and statistical analysis plan have been described in detail elsewhere.[8] Briefly, the HERA trial is an international intergroup open-label phase III randomised trial involving women with centrally confirmed HER2-positive (immunohistochemistry score 3 or fluorescence in-situ hybridisation positive) early stage invasive breast cancer who had completed local regional therapy and a minimum of four courses of predefined standard adjuvant or neoadjuvant chemotherapy. Eligibility criteria included node-positive disease or node-negative disease if the pathological tumour size was larger than 1 cm. Women with locally advanced disease including inflammatory breast cancers were excluded. Women with a left ventricular ejection fraction (LVEF) of less than 55% after completion of chemotherapy and radiotherapy, congestive cardiac failure, or other major cardiac problems[8] were excluded.

The ethics review boards at all the participating institutions approved the study protocol and all patients gave written informed consent.

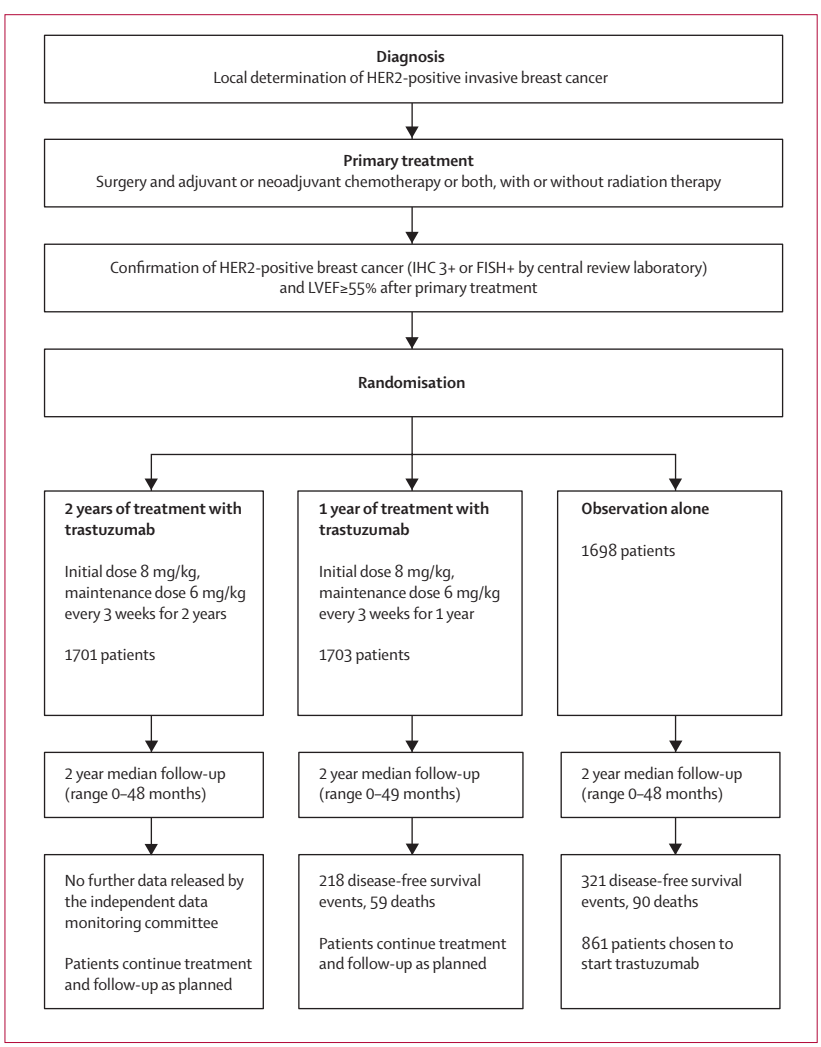

Figure 1: **Trial profile**
FISH+=fluorescence in-situ hybridisation positive. IHC 3+=immunohistochemistry score 3.

Procedures

After local regional therapy (surgery with or without radiotherapy), patients were randomly assigned to one of three groups: observation only, 8 mg/kg trastuzumab given intravenously by 90 minute infusion as a loading dose followed by 6 mg/kg every 3 weeks for 1 year, or the same schedule of trastuzumab for 2 years (not reported here). Randomisation was done within 7 weeks from day 1 of the last chemotherapy cycle or 6 weeks from the end of radiotherapy or definitive surgery, whichever was the last. A minimisation procedure was used with stratification according to region of the world, age, nodal status, title of chemotherapy, and hormone receptor status together with intention to use endocrine therapy.

When a significant disease-free survival in favour of 1 year's treatment with trastuzumab over observation alone emerged with a median follow-up of 1 year,[8] a protocol amendment was made after recruitment had been completed (except for the last five patients) to allow women in the observation group the option of switching to trastuzumab, irrespective of the interval since randomisation. Women who opted to switch were also given the further choice of a secondary randomisation to 1 year versus 2 years of treatment with trastuzumab.

The primary endpoint of the trial was disease-free survival (defined as time from randomisation to the first occurrence of any of the following events: recurrence of breast cancer at any site; the development of ipsilateral or contralateral breast cancer including ductal carcinoma in situ but not lobular carcinoma in situ; second non-breast malignant disease other than basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix; or death from any cause without documentation of a cancer-related event), and the effect of trastuzumab on this endpoint has been described previously.[8] Overall survival was a secondary endpoint; other secondary efficacy endpoints included time to recurrence, time to distant recurrence, and safety, including cardiac safety. Criteria for interrupting or stopping trastuzumab therapy on the basis of cardiotoxicity or other side-effects have been previously described.[8]

Severe congestive heart failure, which does not include death from cardiac causes, was defined as New York Heart Association grade III or IV functional class

confirmed by a cardiologist and a decrease in LVEF of at least 10% below baseline and to less than 50%. Symptomatic congestive heart failure was defined as symptomatic congestive heart failure confirmed by a cardiologist and LVEF less than 50% and a decrease in LVEF of at least 10% from baseline.

A significant LVEF drop was defined as a decrease in LVEF of 10 points or more from baseline to a level below 50 points. A confirmed significant LVEF drop was defined as an asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) significant drop in LVEF which is also confirmed on repeat LVEF assessment about 3 weeks after the first documented drop, or as identified by the cardiac advisory board review.

Statistical analysis

A target accrual of 4482 patients was planned to identify a 23% reduction in the risk of a disease-free survival event with 80% power with a two-sided level of significance of 2·5% for both of the pairwise comparisons: 2 years of treatment with trastuzumab versus observation alone and 1 year of treatment with trastuzumab versus observation alone. 951 endpoint events were required for the final analysis. One interim efficacy analysis was planned after 475 events, the results of which, reviewed by the independent data monitoring committee in April, 2005, resulted in the initial HERA trial publication.[8]

The efficacy analyses were done on an intention-to-treat basis. χ^2 tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values. Kaplan-Meier curves were calculated. Cox proportional hazards regression analysis was used to estimate hazard ratios and 95% CI. Statistical analyses were done with SAS version 8.

In addition to the main intent-to-treat analysis, an analysis that censored women at the time of switching to trastuzumab has also been done to compensate for a potential effect of delayed administration of trastuzumab.

The independent data monitoring committee continues to review data about deaths, compliance, and safety every 6 months. On the basis of a review in March, 2006, they recommended that overall survival results for observation alone versus treatment with trastuzumab for 1 year with a median follow-up of 2 years should be made public. Results for the group of patients treated with trastuzumab for 2 years remain blinded because the comparison with the group treated for 1 year continues to mature. This trial is registered with the European Clinical Trials Database, number 2005–002385–11.

Role of the funding source

The trial was sponsored and funded by Roche. The collection, analysis, and interpretation of the data were done entirely independently, under the auspices of the Breast International Group. The corresponding author led the writing of the paper with input from the HERA executive committee, which includes a Roche representative who was not allowed to influence the paper in any way other than as approved by the executive committee. All authors had access to all the data. The trials' steering committee had final responsibility to submit the manuscript for publication.

Results

5102 women were recruited between December, 2001, and June, 2005, including 1698 in the observation group and 1703 assigned to receive 1 year of treatment with trastuzumab (figure 1). The baseline characteristics of patient tumours and treatment, updated from the

	Observation group (n=1698)	1-year trastuzumab group (n=1703)
Age (years)		
<35	126 (7%)	127 (7%%)
35–49	752 (44%)	756 (44%)
50–59	548 (32%)	548 (32%)
≥60	272 (16%)	272 (16%)
Prior (neo)adjuvant chemotherapy		
No anthracyclines	101 (6%)	101 (6%)
Anthracyclines, no taxanes	1156 (68%)	1154 (68%)
Anthracyclines and taxanes	441 (26%)	448 (26%)
Menopausal status*		
Premenopausal	234 (14%)	257 (15%)
Uncertain	692 (41%)	681 (40%)
Postmenopausal	770 (45%)	765 (45%)
Hormone receptor status		
Negative	843 (50%)	843 (50%)
Positive	855 (50%)	860 (50%)
Nodal status†		
Not assessed (neoadjuvant chemotherapy)	178 (10%)	194 (11%)
Negative	555 (33%)	544 (32%)
1–3	490 (29%)	486 (29%)
≥4	474 (28%)	479 (28%)

Data are number (%). Percentages have been rounded. *Status at randomisation; in the observation group, one patient with unknown menopausal status at randomisation and one patient with missing menopausal status. †One patient with missing nodal status in the observation group.

Table 1: **Baseline patient characteristics**

	Observation group (n=1698)	1-year trastuzumab group (n=1703)
Number of events	321 (19%)	218 (13%)
Deaths	90 (5%)	59 (3%)
Distant event	233 (14%)	152 (9%)
Central nervous system	22 (1%)	26 (2%)
Locoregional event	68 (4%)	45 (3%)
Contralateral breast cancer	9 (0·5%)	7 (0·4%)
Second non-breast malignant disease	8 (0·5%)	6 (0·4%)

Data are number of events (%). Percentages have been rounded.

Table 2: **Site of first disease-free survival event (ITT analysis)**

original publication, are shown in table 1. 97 (5·7%) patients randomly assigned to observation alone and 58 (3·4%) patients randomly assigned to 1 year of treatment with trastuzumab were lost to follow-up.

As of May 15, 2006, 861 women in the observation group had switched to trastuzumab. In the February, 2006, analysis that censored patients at the time of moving to trastuzumab, the median time that had elapsed from the point of switching was 2·6 months. 705 patients originally randomly assigned to observation alone were censored for disease-free survival and overall survival at the date of switching treatment. Results from the censored analysis are much the same as those from the intention-to-treat analysis.

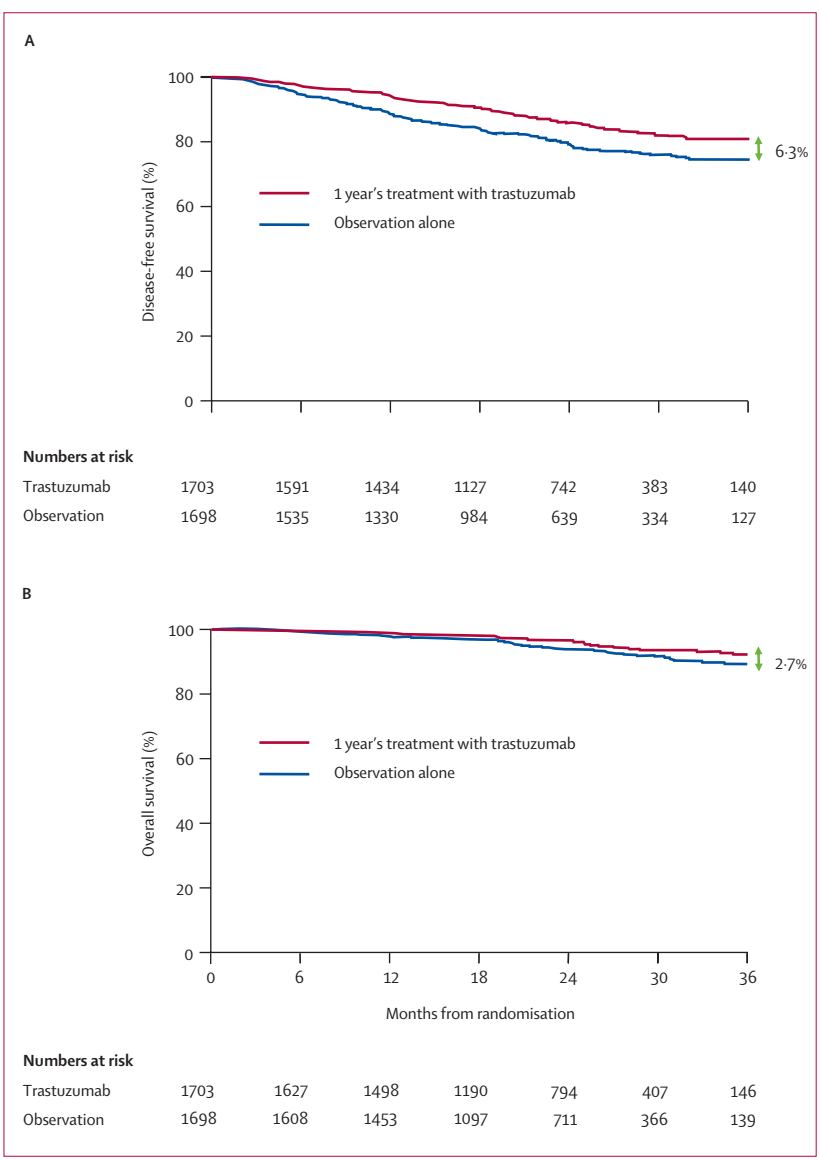

Figure 2: **Kaplan-Meier estimates of disease-free survival and overall survival**
(A) Disease-free survival for 1 year of trastuzumab *vs* observation with a median follow-up of 2 years. (B) Overall survival for 1 year of trastuzumab *vs* observation with a median follow-up of 2 years.

After a median follow-up of 23·5 months (range 0–48 months), 539 disease-free survival events had been recorded in the two groups. Table 2 shows data about the site of first disease-free survival events. The unadjusted HR for the risk of an event in the trastuzumab group compared with the observation group was 0·64 (95% CI 0·54–0·76; p<0·0001 by the log rank test), which corresponds to an absolute disease-free survival benefit of 6·3% (80·6% *vs* 74·3%) at 3 years (figure 2A). The HR for the disease-free survival benefit by censored analysis was 0·63 (0·53–0·75; p<0·0001).

149 deaths occurred in the two groups; more deaths occurred in the observation group than in the trastuzumab group (table 2). The unadjusted HR for the risk of death in the trastuzumab group compared with observation alone was 0·66 (0·47–0·91; p=0·0115 by the log rank test); which corresponds with an absolute overall survival benefit of 2·7% (92·4% *vs* 89·7%) at 3 years (figure 2B). The HR for overall survival by censored analysis was 0·63 (0·45–0·87; p=0·0051).

More distant metastases were reported in the observation group than in the group receiving trastuzumab (table 2); the HR for time to a distant recurrence in the trastuzumab group compared with the observation group was 0·60 (0·49–0·73; p<0·0001 by log rank test). These results correspond to an absolute time to distant recurrence event-free survival benefit of 6·3% at 3 years (85·7% *vs* 79·4%, p<0·0001).

There was no evidence of substantial heterogeneity in the relative treatment effect on disease-free survival between subgroups, and there was no evidence of any subgroup in which trastuzumab was seen to be less efficacious than observation alone (figure 3). All CIs overlap the overall result.

The annualised hazard rates for disease-free survival for both groups from the point of randomisation are shown in figure 4. An increase in risk during the first year for the observation group was seen, although this risk falls in the second year and beyond. Trastuzumab suppresses this increased early risk. Although the HR between the two groups decreases beyond the second year, there continues to be less chance of a disease-free survival event with trastuzumab compared with observation alone at all points up to 3 years.

There were more episodes of at least one grade 3 or grade 4 adverse event and of serious adverse events with trastuzumab than in the observation group (p<0·0001; table 3). The only grade 3 or grade 4 adverse event experienced by five or more patients in the observation group was hypertension (n=5). The grade 3 or grade 4 adverse events experienced by five or more patients in the trastuzumab group were hypertension (12), depression (8), diarrhoea (7), congestive cardiac failure (7), vomiting (6), arthralgia (6), cardiac failure (5), hot flush (5), headache (5), and back pain (5).

There was a higher incidence of fatal adverse events in the trastuzumab group than in the observation group

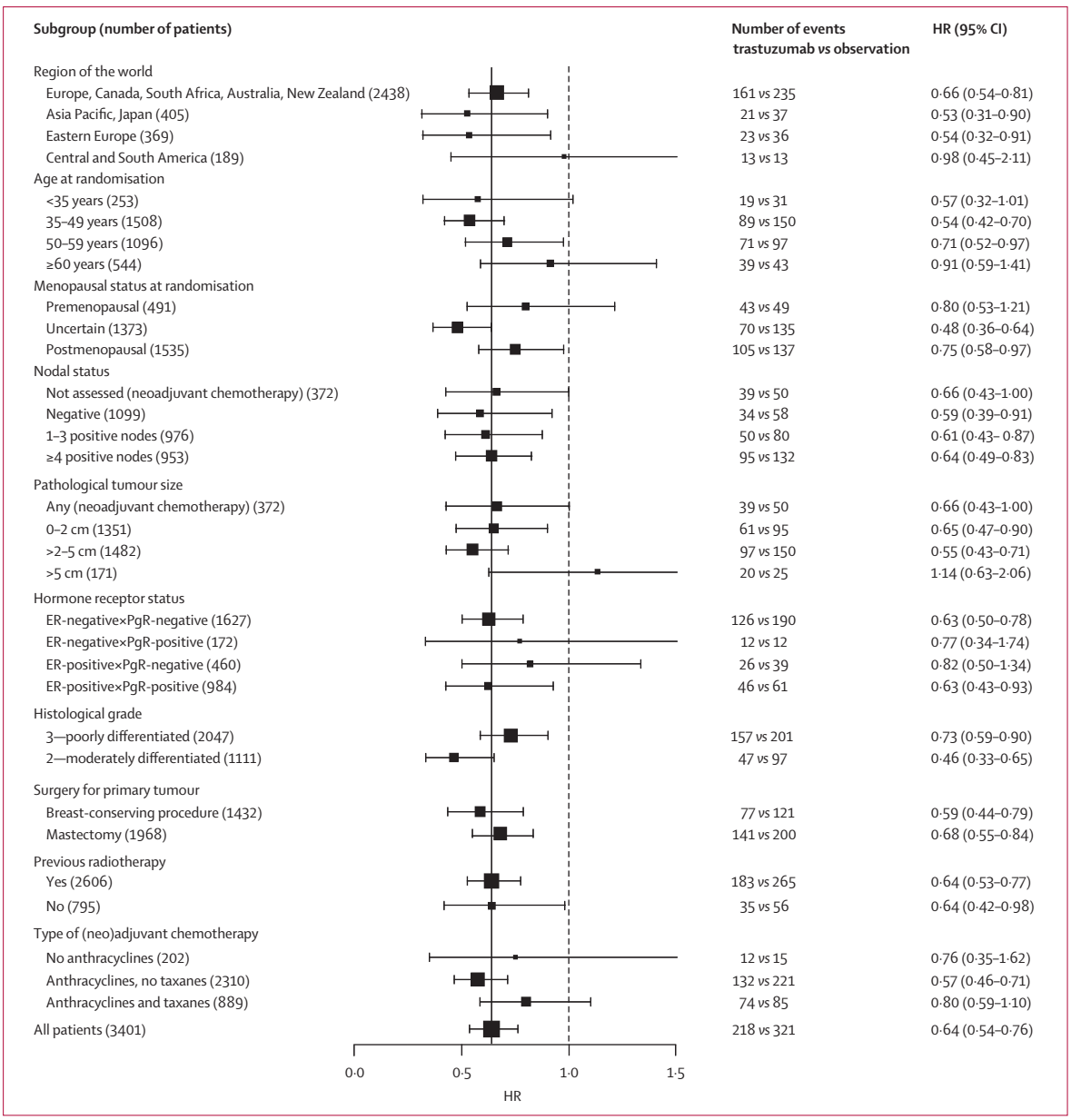

Figure 3: **Exploratory disease-free survival subgroup analysis for 1 year of trastuzumab *vs* observation**

(p=0·1601; table 3). However, the nature of the fatal adverse events did not seem to have any causal relation with trastuzumab. Of the 172 women who stopped trastuzumab prematurely, 115 (6·8%) stopped because of safety issues, 43 (2·5%) because of refusal, and 14 (0·8%) because of other reasons.

As described previously,[13] there was one cardiac death in the observation group and none with trastuzumab. Severe congestive heart failure occurred in more women on trastuzumab than in the observation group (p<0·0001); likewise, symptomatic congestive heart failure (including severe congestive heart failure) occurred in more patients on trastuzumab than in those in the observation group (table 4). Furthermore, a confirmed significant LVEF drop occurred in more women on trastuzumab than in those in the observation group (p<0·0001; table 4). 72 (4·3%) women discontinued trastuzumab because of cardiac problems. A more detailed account of cardiotoxicity in this trial is being prepared.

Discussion

Our results indicate that trastuzumab shows a significant overall survival benefit in early breast cancer over observation alone after chemotherapy. Such a survival benefit after only 2 years of follow-up is unusual in breast cancer trials. For example, adjuvant chemotherapy is of

major importance in the treatment of breast cancer and has achieved a long-term survival benefit of 38% for younger women,[14] but the key early trial for such treatment had not begun to show a substantial survival difference after only 2 years of follow-up,[15] nor have any subsequent chemotherapy trials. In the modern era, the same is true for the aromatase inhibitors, widely deemed to be a major development in adjuvant endocrine therapy.[16–18] Only tamoxifen—the most successful treatment ever developed for breast cancer—showed a similar survival benefit in such a short period.[19] Thus, the early evidence of an overall survival benefit in the HERA trial after only 2 years of follow-up reinforces the importance of trastuzumab in the adjuvant treatment of women with HER2-positive early breast cancer.[20]

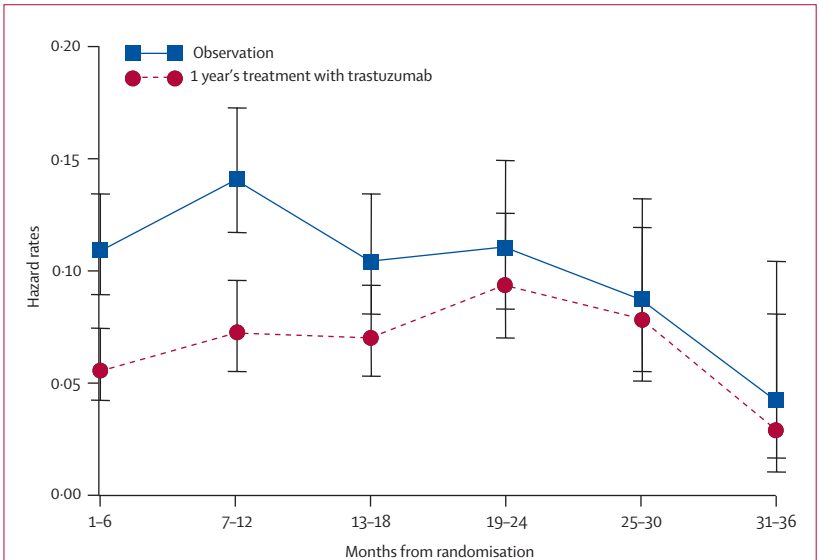

Figure 4: **Annualised disease-free survival hazard rates for 1 year of trastuzumab *vs* observation**

	Observation group (n=1442)*	1-year trastuzumab group (n=1688)*	p value†
Patients with one or more grade 3 or 4 adverse event	88 (6%)	190 (11%)	<0·0001
Patients with one or more serious adverse event	97 (7%)	156 (9%)	0·0103
Fatal adverse event	3 (0·2%)‡	9 (0·5%)§	0·1601
Treatment withdrawals	NA	172 (10%)	..

Data are number of events (%). Percentages have been rounded. NA=not applicable. *271 patients with at least one adverse event after moving to trastuzumab are not included. †Treatment group *vs* observation group. ‡Cardiac failure, suicide, unknown cause of death. §Cerebral haemorrhage, cerebrovascular accident, sudden death, appendicitis, intestinal obstruction, unknown cause of death after a road accident, pulmonary carcinomatous lympangitis, two unknown. The intestinal obstruction occurred after a second occurrence of non-breast malignant disease.

Table 3: **Adverse events**

	Observation (n=1708)	1-year trastuzumab (n=1678)	p value*
Cardiac death	1 (0·1%)	0	1·000
Severe congestive heart failure (NYHA III and IV)†	0	10 (0·6%)	<0·0001
Symptomatic congestive heart failure‡	2 (0·1%)	36 (2%)	<0·0001
Confirmed significant LVEF drop§	9 (0·5%)	51 (3%)	<0·0001
Trastuzumab discontinued due to cardiac problems	NA	72 (4%)	<0·0001

Data are number of events (%). Percentages have been rounded. NA=not applicable. *Treatment group *vs* observation group. †Not including cardiac death. ‡Including severe congestive heart failure but not including cardiac death. §Asymptomatic or mildly symptomatic.

Table 4: **Cardiac safety**

That this survival difference will not be sustained with further follow-up is a possibility; however, there are few precedents for this in work already published on adjuvant therapies for early breast cancer. Furthermore, after the publication of disease-free survival results from HERA with a median follow-up of 12 months,[8] we estimated that the chance of losing statistical significance with longer follow-up was less than 20%. This estimate was calculated on the basis of division of HRs for disease-free survival into a fixed component already observed and a random component, assuming that the risk for the observation group fell to the level seen in the trastuzumab group and follow-up was continued for a further 4 years. Because more events have occurred in the observation group than in the trastuzumab group during the subsequent 12 months, and the HR has fallen for both arms beyond 2 years, the chance of loss of significance remains below 20%. The same arguments pertain for overall survival. The one confounding issue is the recent cross-over of patients in the control group to trastuzumab; it could be that, with longer follow-up, a significant overall survival benefit might be maintained in the censored analysis, but not the intention-to-treat analysis because of this crossover.

The NSABP B-31 trial compared treatment with trastuzumab for 1 year starting concurrently with four courses of paclitaxel after a combination of doxorubicin and cyclophosphamide with the same chemotherapy schedule alone.[9] When data from this trial were combined with results from two similar groups in the NCCTG 9831 trial, a significant overall survival benefit was noted after a median follow-up of 2 years and with an HR of 0·67 in favour of trastuzumab,[9] which is much the same as that recorded here. The consistently high reductions in the risk of breast cancer recurrence of around 50% seen in these two trials, together with that noted in a fourth large adjuvant trastuzumab trial, BCIRG 006,[10] suggest that these results will probably translate into stand-alone survival gains in the near future.

Our exploratory subgroup analysis suggests that all subgroups of women seem to benefit from trastuzumab. In particular, there is so far no significant difference in efficacy between women with node-positive and node-negative disease, nor between those receiving adjuvant compared with neoadjuvant chemotherapy. Whether different patterns of treatment effect emerge for some subgroups with further follow-up remains to be seen.

That the risk of cardiotoxicity remains low is encouraging, and the absence of any substantial evidence of an increase in cumulative cardiotoxicity beyond 1 year has also been shown in the B-31 trial.[21] The overall risk of severe congestive heart failure reported here is lower than

that reported in the B-31 trial (0·6% *vs* 4·1%),[21] as is the proportion of women who stopped treatment because of cardiac problems (4·3% and, of evaluable trastuzumab patients, 15·6%). These findings could be a result of the longer time interval between stopping chemotherapy with anthracyclines and starting trastuzumab in the HERA trial than in B-31, or the requirement of a postchemotherapy LVEF of 55% or more before enrolment in HERA, or both. In this context, one should note that the incidence of cardiotoxicity in the anthracycline followed by trastuzumab group of the BCIRG 006 trial was much the same as that in B-31, but substantially lower in the trastuzumab group that did not receive anthracycline.[10] Thus far, the only data for cardiotoxicity associated with trastuzumab continued for more than a year is in metastatic breast cancer: in one recent study involving 218 patients with a median treatment duration of 21 months and a median follow-up of 32·6 months, 49 (28%) experienced a cardiac event and 19 (10·9%) grade 3 cardiotoxicity.[22] However, most patients improved after withdrawal of trastuzumab and appropriate treatment, and there was only one cardiac death. One should note that these patients would often be less fit than those in HERA and other adjuvant trials because of their metastatic disease, and some would have received a greater cumulative dose of anthracycline chemotherapy.

Two major questions remain for adjuvant trastuzumab. The first is whether trastuzumab started concurrently with taxane chemotherapy (as in the USA trials) is better than trastuzumab starting sequentially after completion of chemotherapy (as here). The NCCTG N9831 trial addresses this issue—this trial includes a third group given sequential trastuzumab. Preliminary data suggest that sequential treatment might be less effective than concurrent treatment,[23] but this was an unplanned comparison with low statistical power, and longer follow-up is needed for confirmation. In this context, one should note that the median time from diagnosis of breast cancer to starting trastuzumab in the HERA trial was 8·5 months, which could have affected efficacy or resulted in some patients with very high-risk disease relapsing before the opportunity arose to enter the trial.

The second issue concerns the duration of trastuzumab treatment. A third group in the HERA trial, in which patients are treated with trastuzumab for 2 years, addresses this issue. That trastuzumab suppresses the increased early hazard rate seen in the observation group during the first year, but has less effect thereafter, might be of relevance (figure 4). This finding supports our decision to compare 2 years of treatment with trastuzumab with 1 year of treatment. However, one should also note that a small Finnish trial involving 232 women has reported a disease-free survival benefit with 9 weeks of trastuzumab treatment given concurrently with chemotherapy at the start of treatment.[11] The HR from this trial (0·42, 95% CI 0·21–0·83; p=0·01) is within the same range as those recorded in trials of trastuzumab treatment for 1 year, but the small number of women involved, together with the wide CI, require confirmatory data.

The data presented here confirm earlier reports that trastuzumab, a rationally designed biological therapy that is targeted against a specific amplified gene (HER2) and its over-expressed receptor protein, is of benefit to women with HER2-positive breast cancer when given after completion of adjuvant chemotherapy. The survival benefit that has emerged over such a short period emphasises the potential of this approach and underlines the importance of developing further specific targeted therapies in breast and other cancers.

Contributors

M Untch was a member of the executive committee and participated in the conduct of the trial and the preparation of the manuscript. M Kaufmann participated in the HERA study with the German GABG-Study Group, of which he is chairman and participated in the conduct of, and recruitment to, the HERA trial as a key investigator. R Bell participated in the concept, management, and conduct of the HERA trial as a member of the executive committee, steering committee, and as an investigator. R I Lopez participated in the conduct of, and recruitment to the HERA trial as a key investigator. M Procter was involved in the statistical analysis. P Mallmann participated in the conduct of, and recruitment to the HERA trial as a key investigator. K Gelmon participated as an investigator, as the representative of the National Cancer Institute of Canada–Clinical Trials Group (NCIC-CTG), and on the trial committee, and contributed to the final version of the manuscript. E Wist was principal investigator in Norway. J Bergh took part in the study planning, was a member of the steering committee, and made comments on a draft version of the manuscript. G Mariani was principal investigator for the Michelangelo group. M J Piccart-Gebhart participated in the design, conduct, and analysis of the trial as chief investigator and chairman of the steering committee. P Sánchez Rovira took part in the conduct of recruitment to the HERA trial as a key investigator. I Smith took part in the planning and execution of the HERA trial, and wrote the first and final drafts of this manuscript. N Wilcken was a member of the steering committee and took part in the writing of the manuscript. A Goldhirsch took part in the study design, conduct, and interpretation of the results. R Coleman took part as an investigator, was leader of the participating EORTC collaborative group, and was a member of the HERA steering committee. A Wardley participated in the conduct of, and recruitment to the HERA trial as a key investigator and helped write the manuscript. S Guillaume was the intergroup and monitoring coordinator. N Harbeck was a member of the German HERA steering committee, and took part in the design, revision, and amendment of the study design. She was a local principal investigator, involved in patient recruitment. J Baselga took part in the design, conduct, patient accrual, and interpretation of the data as a member of the executive committee and as an investigator. M Dowsett was a member of the executive committee and co-chair of the translational research committee. D Cameron was an investigator in the HERA trial, and was a member of the steering and executive committees. As the executive committee member representative for all Breast International Group collaborative groups, he was involved in the day-to-day running of the trial. R D Gelber took part in the design, conduct, analysis, and reporting of the trial in his role as senior statistician. He directed statistical analyses and contributed to the writing of the manuscript. A Feyereislova was a coordinator and reviewed the published data. All authors saw and approved the final version of the manuscript.

Conflict of interest statement

M Untch has received speaker's honoraria from Roche. R Bell has served as an adviser to Roche. In the past 2 years, K Gelmon has been on advisory boards and has received honoraria from Roche, sanofi aventis, Bristol-Myers Squibb, AstraZeneca, Novartis, Pfizer, Lilly, Amgen, Genetech, and GlaxoSmithKline. She has also received research grants from Roche. J Bergh's research group has received research support from Roche, and J Bergh has taken part in advisory boards for Roche. M J Piccart-Gebhart has served on an advisory board on Aromasin, has received consulting fees from GlaxoSmithKline, and an unrestricted educational grant from Roche

on behalf of the Breast International Group. I Smith has received honoraria from Roche for lectures and attendance at advisory boards. N Wilcken has received honoraria from Roche for educational presentations. A Goldhirsch has received honoraria and travel expenses from Roche. A Wardley has received honoraria from Roche for speaking engagements including the use of adjuvant trastuzumab. He has also received travel grants from Roche and worked and done a small amount of advisory work for Roche. N Harbeck has received speaker's honoraria from Roche and received the investigators fee from the German Breast Group. J Baselga is a member of the Roche herceptin advisory board. M Dowsett has received fees for attending advisory board meetings and giving ad-hoc lectures for Roche. D Cameron has received research funding from Roche (separate to that for the conduct of this trial), and has also received honoraria and consultancy fees from Roche. R D Gelber declares that Roche provided financial support for the Breast European Adjuvant Study Team (BrEAST), which in turn provided him with partial salary support. A Feyereislova is an employee of Roche. R Coleman, M Kaufmann, S Guillaume, M Procter, P Mallmann, E Wist, G Mariani, P Sanchez Rovira, and R I Lopez declare that they have no conflict of interest.

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