# Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial

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## Summary

**Background** Treatment with adjuvant trastuzumab for 1 year improves disease-free survival and overall survival in patients with human epidermal growth factor receptor 2 (HER2)-positive early breast cancer. We aimed to assess disease-free survival and overall survival after a median follow-up of 4 years for patients enrolled on the Herceptin Adjuvant (HERA) trial.

**Methods** The HERA trial is an international, multicentre, randomised, open-label, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant, adjuvant chemotherapy, or both in patients with HER2-positive early breast cancer. The primary endpoint was disease-free survival. After a positive first interim analysis at a median follow-up of 1 year for the comparison of treatment with trastuzumab for 1 year with observation, event-free patients in the observation group were allowed to cross over to receive trastuzumab. We report trial outcomes for the 1-year trastuzumab and observation groups at a median follow-up of 48·4 months (IQR 42·0–56·5) and assess the effect of the extensive crossover to trastuzumab. Our analysis was by intention-to-treat. The HERA trial is registered with the European Clinical Trials Database, number 2005-002385-11.

**Findings** The HERA trial population comprised 1698 patients randomly assigned to the observation group and 1703 to the 1-year trastuzumab group. Intention-to-treat analysis of disease-free survival showed a significant benefit in favour of patients in the 1-year trastuzumab group (4-year disease-free survival 78·6%) compared with the observation group (4-year disease-free survival 72·2%; hazard ratio [HR] 0·76; 95% CI 0·66–0·87; p<0·0001). Intention-to-treat analysis of overall survival showed no significant difference in the risk of death (4-year overall survival 89·3% *vs* 87·7%, respectively; HR 0·85; 95% CI 0·70–1·04; p=0·11). Overall, 885 patients (52%) of the 1698 patients in the observation group crossed over to receive trastuzumab, and began treatment at median 22·8 months (range 4·5–52·7) from randomisation. In a non-randomised comparison, patients in the selective-crossover cohort had fewer disease-free survival events than patients remaining in the observation group (adjusted HR 0·68; 95% CI 0·51–0·90; p=0·0077). Higher incidences of grade 3–4 and fatal adverse events were noted on 1-year trastuzumab than in the observation group. The most common grade 3 or 4 adverse events, each in less than 1% of patients, were congestive cardiac failure, hypertension, arthralgia, back pain, central-line infection, hot flush, headache, and diarrhoea.

**Interpretation** Treatment with adjuvant trastuzumab for 1 year after chemotherapy is associated with significant clinical benefit at 4-year median follow-up. The substantial selective crossover of patients in the observation group to trastuzumab was associated with improved outcomes for this cohort.

**Funding** F Hoffmann-La Roche, Michelangelo Foundation.

## Introduction

The human epidermal growth factor receptor 2 (HER2) gene is amplified, overexpressed, or both in 15–25% of breast cancers[1,2] and is associated with aggressive disease.[3] Trastuzumab (Herceptin; F Hoffmann-La Roche, Basel, Switzerland), a humanised monoclonal antibody that targets the extracellular domain of the HER2 receptor,[4] has established clinical benefits in women with HER2-positive breast cancer in metastatic and early disease settings.[5–15]

The Herceptin Adjuvant (HERA) trial (Breast International Group 01-01) is an ongoing, international, multicentre, randomised, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant/adjuvant chemotherapy in women with HER2-positive early breast cancer. 5102 women were enrolled into the HERA trial, and a planned interim analysis at a median follow-up of 1 year showed that the addition of trastuzumab to standard adjuvant chemotherapy significantly improved disease-free survival compared with chemotherapy alone (hazard ratio [HR] 0·54; 95% CI 0·43–0·67).[9] These results led to a protocol amendment, which allowed patients in the observation

group with left ventricular ejection fraction (LVEF) of 55% or greater who had not relapsed to cross over to treatment with trastuzumab. An updated intention-to-treat analysis at a median follow-up of 2 years showed that addition of trastuzumab was associated with a significant improvement in disease-free survival (HR 0·64; 95% CI 0·54–0·76) and overall survival (HR 0·66; 95% CI 0·47–0·91) compared with chemotherapy alone.[12]

We report new data on the HERA trial 1-year trastuzumab versus observation comparison at a median follow-up of 4 years, and assess the effect on outcome measures of the extensive crossover of patients from the observation group to treatment with trastuzumab.

## Methods

### Participants

The HERA trial design, eligibility criteria, randomisation, treatment plan, follow-up and monitoring, and statistical analyses have been described elsewhere.[9,12] Briefly, from Dec 7, 2001, to June 20, 2005, the study recruited 5102 women with HER2-positive (centrally confirmed overexpression or amplification) early-stage invasive breast cancer who had completed locoregional therapy (surgery with or without radiotherapy) and received at least four cycles of chemotherapy (neoadjuvant, adjuvant, or both). Patients were randomly assigned to three groups: observation, trastuzumab for 1 year, and trastuzumab for 2 years. Trastuzumab therapy comprised intravenous infusions over 90 min every 3 weeks (initial loading dose 8 mg/kg; 6 mg/kg thereafter). All patients gave written, informed consent. The study protocol was approved by ethics review boards at all participating centres.

### Randomisation and masking

Random assignment to one of the three groups on a 1:1:1 basis 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 last. A minimisation procedure, following the methods of Pocock and Simon,[17] was used with stratification by age, worldwide region, nodal status, type of chemotherapy, and hormone-receptor status, together with intention to use endocrine therapy. Randomisation was done at the site under the responsibility of the investigator with an interactive voice response system. The HERA trial is open label.

### Procedure

The primary endpoint was disease-free survival; secondary endpoints included overall survival, time to recurrence, time to distant recurrence, and safety (including cardiac safety). Cardiac events (including severe congestive heart failure, symptomatic congestive heart failure, significant LVEF drop, and confirmed significant LVEF drop), safety assessments, and criteria for interrupting or stopping treatment with trastuzumab have been described previously.[9,16] Quality-of-life data were not recorded.

Early outcomes for treatment with trastuzumab for 1 year versus observation have been reported at a median follow-up of 1 year[9] and 2 years.[12] Based on the significant observed benefit of 1 year of trastuzumab,[9] a protocol amendment allowed patients in the observation group who were alive and disease free as of May 16, 2005, to cross over to treatment with trastuzumab (irrespective of the interval since randomisation). All eligible patients in the observation group (disease free and LVEF of 55% or greater) received standard written information regarding the positive outcome of the primary endpoint and were invited to cross over to treatment with trastuzumab for 1 year or to accept random assignment to receive treatment with trastuzumab for 1 or 2 years. The decision to select crossover seemed to be individually based, because clear patterns of institutional differences were not detected.

After the second planned interim analysis of the 1-year versus 2-year trastuzumab comparison on Oct 20, 2008, the independent data monitoring committee recommended that the trial continue as planned, without release of the data for the 2-year trastuzumab group, until the final event-driven analysis. Data updates for the 1-year trastuzumab versus observation group comparison are planned for every 2 years, and here we report such an update at a median of 48·4 months.

### Statistical analyses

Efficacy analyses were by intention to treat. Kaplan-Meier curves were estimated for time-to-event endpoints. For disease-free and overall survival comparisons between treatment groups, Cox proportional hazards regression analysis was used to estimate HRs, with 95% CIs and p values.[18] Statistical analyses used SAS software (version 9.2).

Follow-up was estimated with reverse censoring for overall survival.[19] For disease-free and overall survival, patient-years of follow-up in the intention-to-treat observation group were calculated from randomisation (or from crossover for the selective-crossover cohort) to the date of event or last contact. Cumulative incidence estimates were used for the selective crossover probability by time from randomisation, to control competing risks.[20] We also did censored analyses for disease-free and overall survival, with follow-up censored at date of crossover for the selective-crossover cohort.

To assess if a treatment effect was apparent in the selective-crossover cohort, a time-varying covariate Cox model for disease-free survival was applied to the observation group.[18] This model, which estimated the average HR, addressed the differing length of follow-up of patients from randomisation to crossover and the time-varying entry into the selective-crossover cohort. The classification into the selective-crossover cohort or the cohort remaining in the observation group is a

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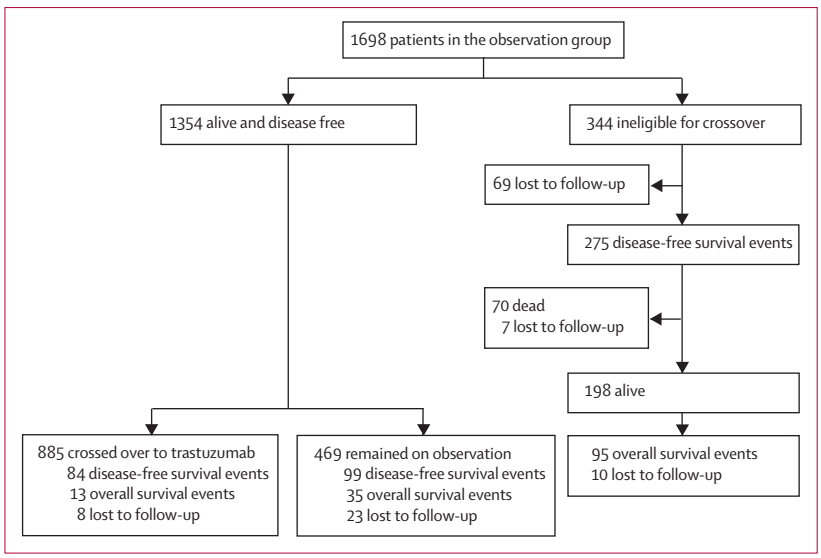


***Figure 1:*** **Flowchart of patients in the observation group by status on May 16, 2005**
Of the 885 patients who selectively crossed over to treatment with trastuzumab, 621 either elected or were randomly assigned to receive treatment with trastuzumab for 1 year, while 263 were randomly assigned to receive the drug for 2 years. One patient received treatment for an unknown scheduled period.

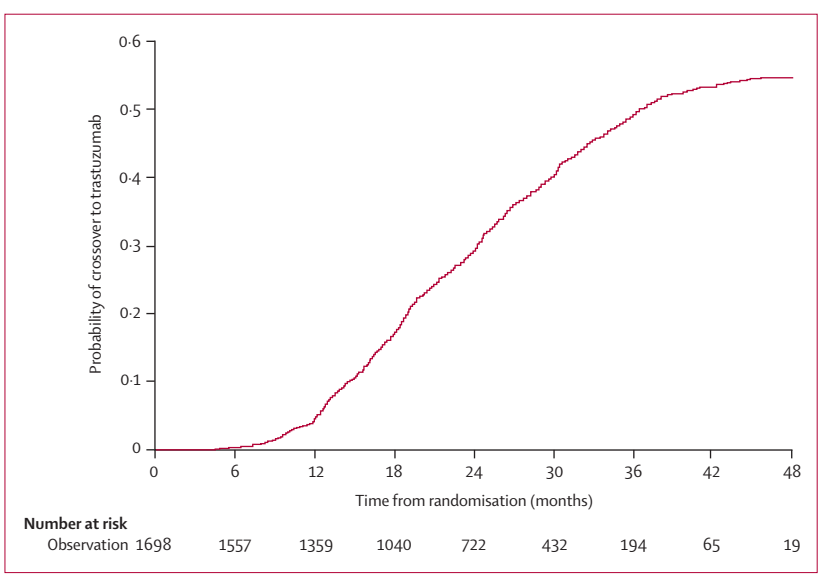


***Figure 2:*** **Cumulative probability of selective crossover to trastuzumab (observation group) by months from randomisation on the basis of competing risks**
The competing risks were a disease-free survival event and registration to remain in the observation group. Median time from randomisation to first dose was 22·8 months (range 4·5–52·7) and median follow-up time from first dose was 29·1 months (0·8–34·5). The proportion of patient-years of follow-up after selective crossover in the observation intention-to-treat group was 33·8% for disease-free survival and 30·9% for overall survival.

time-varying covariate that corresponds to an intervening event (ie, trastuzumab treatment) that can irreversibly alter a patient's risk during follow-up.[21] The time-dependent covariate considers each patient to be in the observation group until trastuzumab is started. Inclusion of baseline covariates in the model enabled adjustment for effects of known confounders, noting that the effect of unmeasured confounders cannot be ruled out. The HERA trial is registered with the European Clinical Trials Database, number 2005-002385-11.

### Role of the funding source

The HERA trial was sponsored and funded by Roche. Collection, analysis, and interpretation of data were done independently under the auspices of the Breast International Group (EA, MJP, UD, RG, GS, MP). The corresponding author led the writing of our report, with input from the HERA executive committee (LG, RG, EA, MU, IS, JB, CJ, DC, MJP-G, RB; which included a minority Roche representation). All authors had access to all the data. The trial steering committee was responsible for the final decision to submit the report for publication.

## Results

Figure 1 shows the flow of patients in the observation group on May 16, 2005. The HERA trial population in our report comprises 1698 patients randomly assigned to the observation group and 1703 to the 1-year trastuzumab group. In the observation arm, 1354 patients were alive and disease free as of May 16, 2005, and, therefore, eligible for selective crossover to trastuzumab. Of these patients, 885 (65%) crossed over to trastuzumab, corresponding to 52% (885 of 1698) of those randomly assigned to observation. Crossover was within 9 months of the protocol amendment in 781 (88%) of 885 patients. Median time from randomisation to first dose of trastuzumab in the selective-crossover cohort was 22·8 months (range 4·5–52·7; figure 2), which corresponds to a median time from original diagnosis of 30·9 months (range 9·1–58·3). Median follow-up time from the start of treatment with trastuzumab was 29·1 months (range 0·8–34·5).

Table 1 shows the baseline characteristics for the observation and trastuzumab groups and for the observation-group cohorts with and without selective crossover. Characteristics were well balanced between the two randomly assigned groups. In the observation group, patients in the selective-crossover cohort compared with patients remaining on observation were more likely to be younger, to have received both anthracyclines and taxanes, and, to a lesser extent, to be premenopausal, have hormone-receptor-positive disease, and have node-positive disease.

At the clinical cutoff date (June 9, 2008), median follow-up was 48·4 months (range 0–74·9; IQR 42·0–56·5). In the observation group, 33·8% of the intention-to-treat patient-years on follow-up for disease-free survival were derived from the crossover cohort after the start of treatment with trastuzumab.

Of 827 disease-free survival events recorded, 458 (27·0% event rate) were in the 1698 patients randomly assigned to the observation group and 369 (21·7%) in the 1703 patients randomly assigned to the 1-year trastuzumab

group. First disease-free survival events included distant recurrence as the most common (320 in the observation group [18·8% event rate] *vs* 251 on 1-year trastuzumab [14·7%]), with 32 versus 37 CNS events; locoregional recurrence (100 [5·9%] *vs* 79 [4·6%]); contralateral breast cancer (19 [1·1%] *vs* 14 [0·8%]); second non-breast malignancy (14 [0·8%] *vs* 19 [1·1%]); and death without previous recurrence (5 [0·3%] *vs* 6 [0·4%]). Kaplan-Meier estimates of the 4-year disease-free survival were 78·6% for 1-year trastuzumab versus 72·2% for the observation group. The unadjusted HR for risk of a disease-free survival event for patients randomly assigned to 1-year trastuzumab compared with those assigned to the observation group was 0·76 (95% CI 0·66–0·87; p<0·0001; figure 3).

182 patients assigned to receive 1-year trastuzumab and 213 in the observation group died; the Kaplan-Meier estimates of the 4-year overall survival were 89·3% (95% CI 87·6–90·8) versus 87·7% (86·0–89·3). The unadjusted HR for risk of death was 0·85 (95% CI 0·70–1·04; p=0.11).

Figure 4 presents a summary of the intention-to-treat results from the previous two protocol-specified analyses[9,12] and our present analysis. Overall, intention-to-treat analyses for disease-free and overall survival are potentially biased in favour of the observation group, because this group includes the selective-crossover cohort who received trastuzumab (figure 3).

In the censored analyses, disease-free and overall survival data were censored for the 885 patients in the selective-crossover cohort at time of crossover. Longer follow-up of the observation group is increasingly representing the cohort without selective crossover—ie, the 198 patients ineligible for crossover due to a previous disease-free survival event along with the 469 patients eligible for crossover who remained on observation (figure 1).

With censoring, the Kaplan-Meier estimates of the 4-year disease-free survival for the observation group decreased to 71·7% (figure 3). The unadjusted HR for 1-year trastuzumab versus the censored observation group was 0·69 (95% CI 0·59–0·79; p<0·0001). The censored 4-year overall survival Kaplan-Meier estimate for the observation group decreased to 81·5% (figure 3) and the unadjusted HR for 1-year trastuzumab versus the censored observation group was 0·53 (95% CI 0·44–0·65; p<0·0001). 95 (48%) of 198 patients ineligible for crossover died, and 35 (8%) of 469 eligible patients who chose to remain on observation died. Thus, censoring of the event-free, selective-crossover cohort increased the relative proportion of post-disease-free survival-event patients over time in the residual observation-group cohort. With a higher expected death rate in these patients, the censored analysis for overall survival (figure 3) is strongly biased in favour of 1-year trastuzumab.

We used a time-varying covariate Cox model for disease-free survival to explore if patients in the observation group who crossed over had a different course of disease compared with those who remained on observation. The estimated unadjusted HR for risk of a disease-free survival event in the selective-crossover cohort compared with the cohort remaining on observation, at similar follow-up times from randomisation, was 0·69 (95% CI 0·52–0·92; p=0·011).

With adjustments for known confounders (age, type of previous chemotherapy, hormone-receptor status, and nodal status) in a multivariate time-varying covariate Cox model, the estimated HR significantly favoured selective crossover (p=0·0077; figure 5). Figure 6 shows the annualised hazard rates for disease-free survival in the remaining-in-observation and selective-crossover cohorts from randomisation up to 48 months.

Table 2 shows details of National Cancer Institute Common Toxicity Criteria grade 3 or 4 adverse events, those deemed serious, fatal adverse events, and information on cardiac endpoints for the overall safety-analysis population and the remaining-in-observation and selective-crossover cohorts. Higher incidences of grade 3–4 and fatal adverse events were recorded on

| | Intention-to-treat population | | Intention-to-treat observation group (alive and disease free after May 16, 2005) | |
|---|---|---|---|---|
| | 1-year trastuzumab (n=1703) | Observation (n=1698) | No selective crossover (n=469) | Selective crossover (n=885) |
| **Age (years)** | | | | |
| <35 | 128 (8%) | 126 (7%) | 27 (6%) | 63 (7%) |
| 35–49 | 756 (44%) | 753 (44%) | 195 (42%) | 393 (44%) |
| 50–59 | 547 (32%) | 546 (32%) | 140 (30%) | 302 (34%) |
| ≥60 | 272 (16%) | 273 (16%) | 107 (23%) | 127 (14%) |
| **Previous (neo)adjuvant chemotherapy** | | | | |
| No anthracyclines | 101 (6%) | 101 (6%) | 33 (7%) | 49 (6%) |
| Anthracyclines, no taxanes | 1154 (68%) | 1156 (68%) | 342 (73%) | 585 (66%) |
| Anthracyclines and taxanes | 448 (26%) | 441 (26%) | 94 (20%) | 251 (28%) |
| **Menopausal status*** | | | | |
| Uncertain | 684 (40%) | 692 (41%) | 171 (36%) | 369 (42%) |
| Premenopausal | 258 (15%) | 234 (14%) | 55 (12%) | 125 (14%) |
| Postmenopausal | 761 (45%) | 770 (45%) | 243 (52%) | 390 (44%) |
| **Hormone-receptor status†** | | | | |
| Negative | 843 (50%) | 843 (50%) | 234 (50%) | 407 (46%) |
| Positive | 860 (50%) | 855 (50%) | 235 (50%) | 478 (54%) |
| **Nodal status‡** | | | | |
| Not assessed (neoadjuvant chemotherapy) | 194 (11%) | 178 (10%) | 46 (10%) | 80 (9%) |
| Negative | 544 (32%) | 555 (33%) | 172 (37%) | 306 (35%) |
| 1–3 positive | 486 (29%) | 490 (29%) | 131 (28%) | 274 (31%) |
| ≥4 positive | 479 (28%) | 474 (28%) | 120 (26%) | 225 (25%) |

*Status at randomisation; in the observation group, one patient with unknown menopausal status at randomisation and one patient with missing menopausal status. †According to local assessment. One patient in the trastuzumab arm had unknown oestrogen receptor status and progesterone receptor-positive status. ‡One patient with missing nodal status in the observation group.

***Table 1:*** **Baseline patient and tumour characteristics**

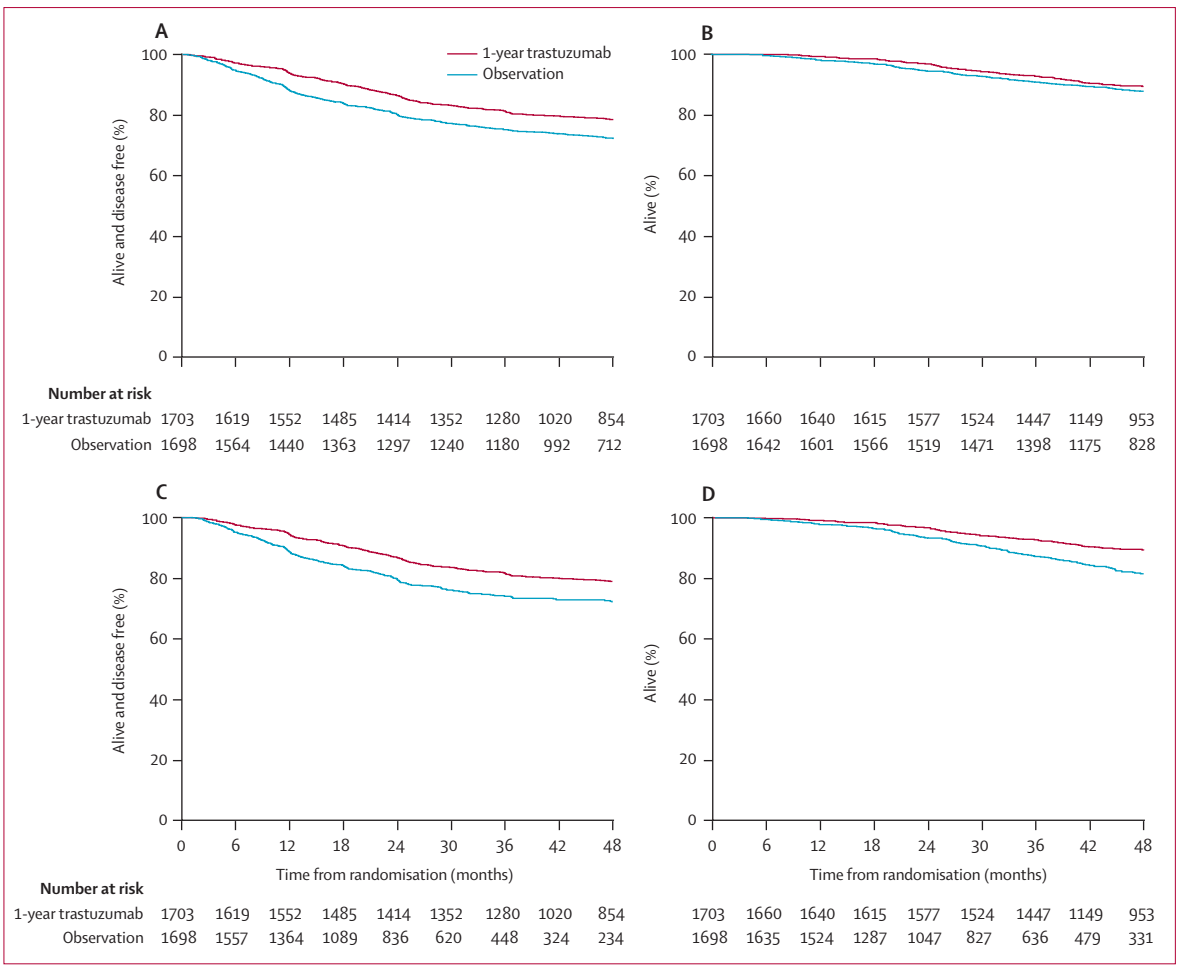


***Figure 3:*** **Kaplan-Meier estimates of disease-free and overall survival at 4-year median follow-up for 1-year trastuzumab versus observation**
Disease-free survival intention-to-treat analysis (A), overall survival intention-to-treat analysis (B), disease-free survival censored analysis (C), and overall survival censored analysis (D).

1-year trastuzumab than in the observation group (censored at crossover).

As reported previously,[9] there was one cardiac death in the observation group. More patients on 1-year trastuzumab than the observation group had symptomatic congestive heart failure and a confirmed significant LVEF drop. In the selective-crossover cohort associated with the delayed trastuzumab treatment, compared with 1-year trastuzumab, there were fewer cases of symptomatic congestive heart failure and confirmed significant LVEF drop (table 2).

The most common grade 3 or 4 adverse events in the 1-year trastuzumab safety-analysis population (1682 patients), observation safety-analysis population (1719), and selective-crossover group (885), respectively, each in fewer than 1% of patients, were cardiac failure congestive (14, 1, 1), hypertension (14, 7, 3), arthralgia (8, 5, 1), back pain (6, 4, 3), central-line infection (6, 0, 4), hot flush (6, 4, 1), headache (4, 3, 3), and diarrhoea (6, 0, 4). There were no grade 3 or 4 adverse events in more than one patient in the no-crossover group.

## Discussion

The HERA trial results confirm that treatment with adjuvant trastuzumab for 1 year is associated with persisting benefits in women with HER2-positive early breast cancer (panel). The significant disease-free survival benefit originally reported at 1-year median follow-up is sustained at 4-year median follow-up, despite the substantial crossover of patients in the observation group to treatment with trastuzumab. The overall-survival benefit is no longer statistically significant by intention-to-treat analysis.

The observed attenuation in efficacy of trastuzumab over time is partly because more than half (885 [52%] of 1698) of patients in the observation group crossed over to receive trastuzumab. This effect was not recorded at 2-year median follow-up, probably because of the short duration of follow-up after crossover at that time (median 2·6 months *vs* 29·1 months in this analysis).

We cannot precisely establish the effect of this extensive crossover on outcomes. A confounding factor is the

selection of patients for crossover was not randomised and that crossover patients had to be free of early disease-free survival events, the very events that drove the protocol amendment to allow crossover[9] and were required for safety to have an LVEF of 55 or greater. We have referred to the process as selective crossover to emphasise the lack of randomisation. The other large trials assessing 1-year adjuvant trastuzumab and reporting sustained efficacy had a much lower degree of crossover. The Breast Cancer International Research Group 006 trial assessing trastuzumab combined with either docetaxel after doxorubicin/cyclophosphamide (AC–TH) or docetaxel plus carboplatin (TCarboH), with a control arm of doxorubicin/cyclophosphamide/docetaxel (ACT), did not permit or facilitate crossover, and only 1·6% of patients in the control group crossed over to trastuzumab. At the third planned efficacy analysis (median follow-up of 5·5 years), AC–TH and TCarboH were each associated with statistically significant improvements in disease-free survival (AC–TH HR 0·64; 95% CI 0·53–0·78; p<0·001; TCarboH HR 0·75; 95% CI 0·63–0·90; p=0·04) and overall survival (AC–TH HR 0·63; 95% CI 0·48–0·81; p<0·001; TCarboH HR 0·77; 95% CI 0·60–0·99; p=0·038) compared with ACT.[15] In the combined analysis of the North Central Cancer Treatment Group trial N9831 and the National Surgical Adjuvant Breast and Bowel Project trial B-31, 20·9% of patients in the control group crossed over to trastuzumab. An updated efficacy analysis (median follow-up of 2·9 years) showed that combining trastuzumab with paclitaxel after doxorubicin/cyclophosphamide (AC) significantly improved disease-free (HR 0·49; 95% CI 0·41–0·58; p<0·0001) and overall survival (HR 0·63; 95% CI 0·49–0·81; p=0·0004)

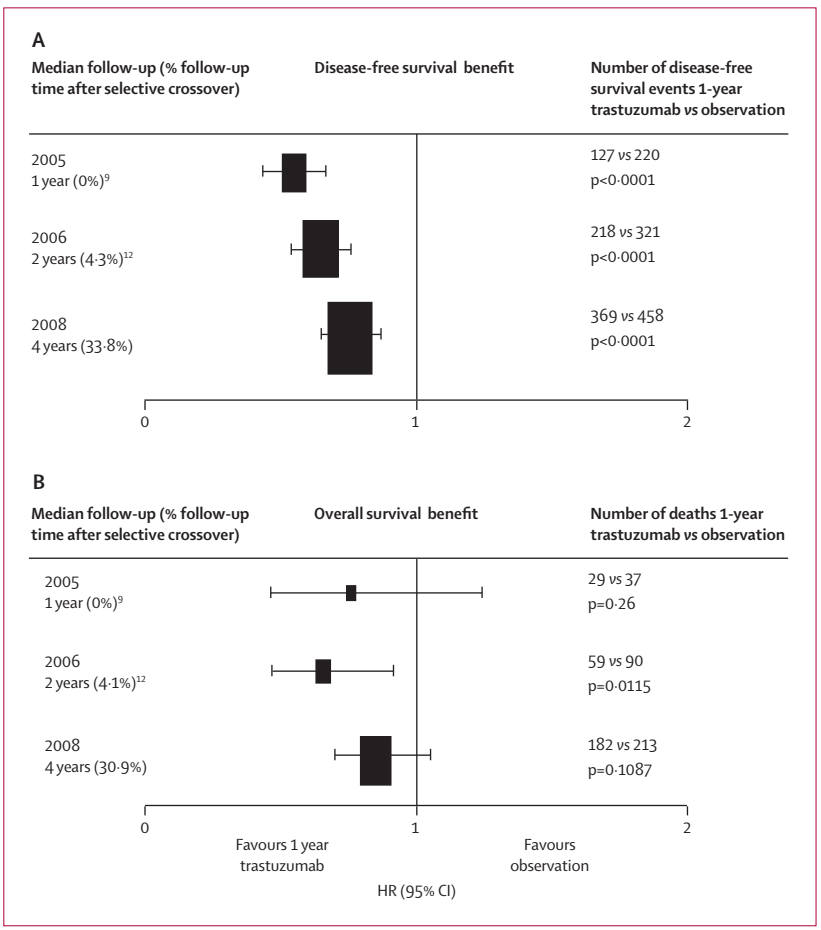


***Figure 4:*** **Summary of disease-free (A) and overall survival (B) intention-to-treat analyses for 1-year trastuzumab versus observation at the three protocol-specified analysis time points**
HR=hazard ratio.

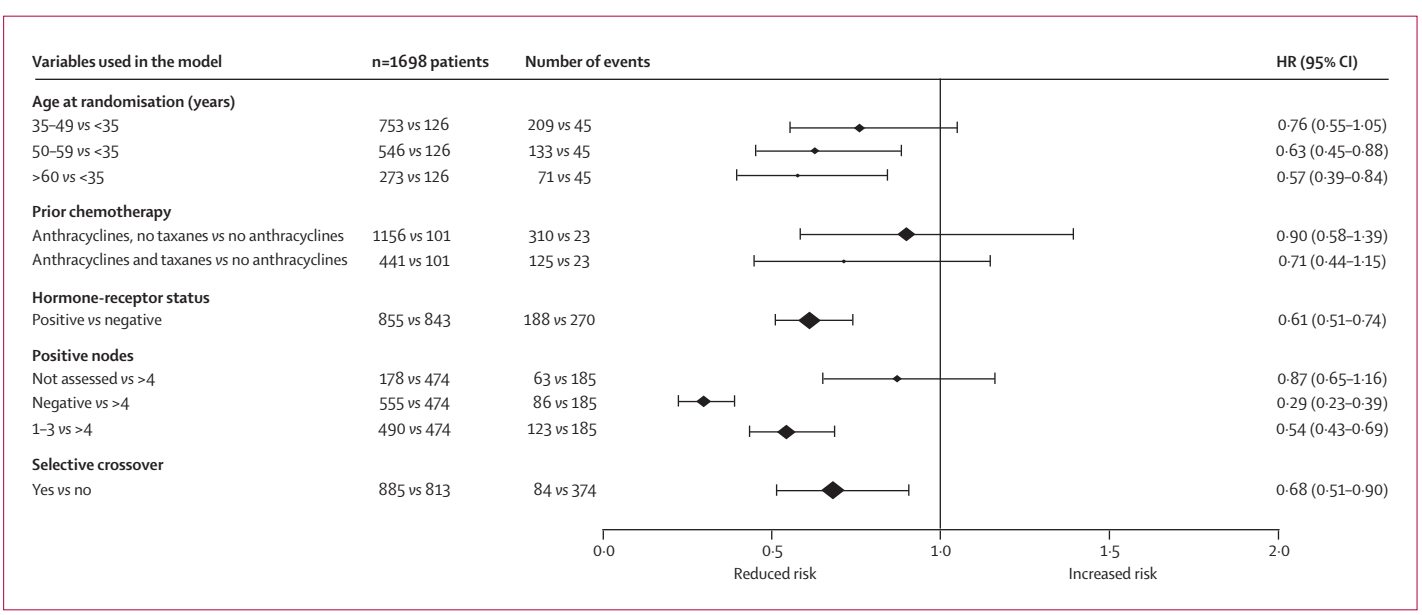


***Figure 5:*** **Forest plot from multivariate time-varying Cox model for disease-free survival in observation-only treatment arm**
HR=hazard ratio.

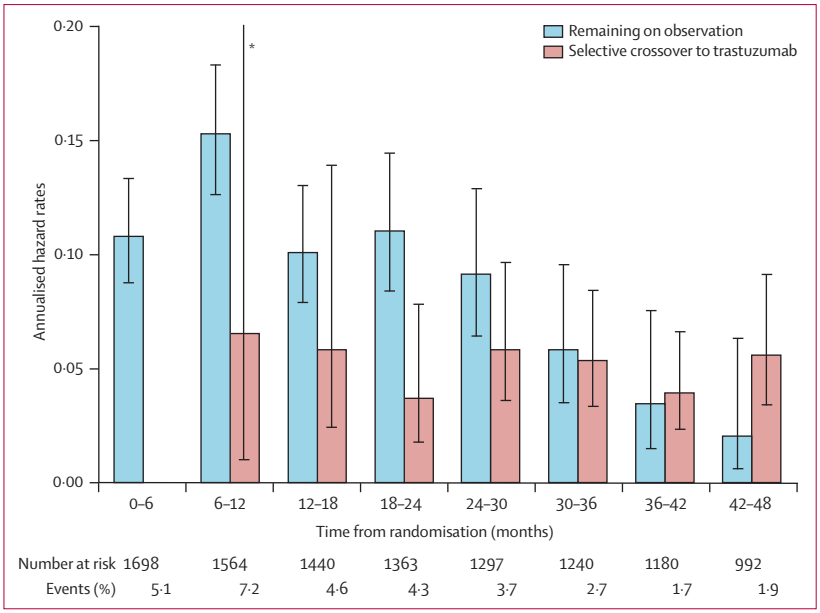


***Figure 6:*** **Annualised disease-free survival hazard rates for the crossover and observation groups**
Rates are the number of disease-free survival events while in the group in the specific 6-month interval divided by the total follow-up time (in years) in the group during the 6-month interval. Whiskers depict the 95% CIs. *Only one event in the selective-crossover cohort.

| | Safety analysis population | | Intention-to-treat observation group (alive and disease free after May 16, 2005) | |
|---|---|---|---|---|
| | 1-year trastuzumab (n=1682) | Observation* (n=1719) | No selective crossover† (n=469) | Selective crossover‡ (n=885) |
| **Adverse events** | | | | |
| Patients with ≥1 grade 3 or 4 adverse event | 239 (14%) | 131 (8%) | 19 (4%) | 80 (9%) |
| Patients with ≥1 serious adverse event | 199 (12%) | 129 (8%) | 19 (4%) | 79 (9%) |
| Fatal adverse event | 12 (1%)§ | 6 (0%)¶\|\| | 2 (0%)\|\| | 1 (0%)** |
| Treatment withdrawals | 176 (11%) | NA | NA | 103 (12%) |
| **Cardiac endpoints** | | | | |
| Cardiac death | 0 | 1 (0%) | 0 | 0 |
| Symptomatic congestive heart failure (II, III, and IV)†† | 33 (2%)‡‡ | 2 (0%) | 1 (0%) | 9 (1%) |
| Confirmed significant LVEF drop§§ | 62 (4%) | 13 (1%) | 5 (1%)¶¶ | 26 (3%) |
| Trastuzumab discontinued due to cardiac problems | 87 (5%) | NA | NA | 43 (5%) |
| Any type of cardiac endpoint | 75 (5%) | 14 (1%) | 5 (1%) | 26 (3%) |

LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. *Observation patients who received trastuzumab were censored from the date of starting trastuzumab. †Occurrence after May 16, 2005. ‡Occurrence after date of starting trastuzumab. §Cerebral haemorrhage, cerebrovascular accident, sudden death, appendicitis, unknown cause of death after road accident, malignant melanoma, meningioma, metastatic renal-cell carcinoma, uterine cancer, congestive cardiac failure, rectal cancer, and one unknown. ¶Cardiac failure, suicide, pulmonary sepsis, and pancreatic carcinoma. ||Myocardial infarction and pulmonary embolism. **Haemorrhagic stroke. ††Not including cardiac death. ‡‡20 NYHA II and 13 NYHA III and IV. §§Asymptomatic or mildly symptomatic. ¶¶For three patients, LVEF drop happened soon after the release of trial results and might have influenced their decisions.

***Table 2:*** **Adverse events and cardiac endpoints by safety analysis population and observation-arm cohorts after May 16, 2005**

compared with chemotherapy alone.[13] A recent update of the N9831 trial at 5·5-year median follow-up reported the superiority of its sequential group over control (disease-free survival HR 0·70; 95% CI 0·57–0·86; p=0·0005),[22] thus confirming the clinical benefit of the sequential approach used in the HERA trial. In N9831, there was a suggestion that concurrent administration of trastuzumab might improve disease-free survival compared with the sequential approach (HR 0·75) but the difference was not significant (p=0·019, with a prespecified boundary for significance of p=0·00116).

Our censored analysis, which removed all crossover patients' follow-up after the start of treatment with trastuzumab, assessed the treatment effect of crossover by ostensibly removing this confounding factor. Our findings based on this analysis are heavily biased in favour of 1-year trastuzumab, particularly with regard to overall survival, because of the retention of all post-disease-free survival patients in the cohort remaining on observation while attenuating the overall group number.

The extent of crossover in the HERA trial is not unique; in fact, crossovers of this size are common in recent trials. We assessed if patients who crossed over to trastuzumab had a different disease course than those who remained on observation with a time-varying Cox analysis for disease-free survival in the observation group. Although exploratory, our findings suggest a difference for the risk of a disease-free survival event for the cohort receiving trastuzumab starting at a median of 23 months from randomisation.

As reported previously,[9,12,16] the overall incidence of cardiac events in the HERA trial remains low with longer follow-up. Reports of cardiac events in other large trials of treatment with adjuvant trastuzumab have also remained low.[15,23] Risk factors associated with the development of trastuzumab-related cardiac events are well documented and include body-mass index and baseline LVEF.[16] Other possible risk factors identified include hypertension, diabetes, smoking status, and hypothyroidism.

Reported cardiac events experienced in crossover patients were less common and of lower severity than with upfront trastuzumab, but this comparison was not prospectively planned nor based on randomised groups, and the findings should not be thought conclusive. The lower incidence could possibly be due to the longer interval between the start of anthracycline and trastuzumab, since concomitant administration of these drugs has been associated with increased cardiac dysfunction.[24]

In summary, these findings confirm that adjuvant trastuzumab given sequentially to chemotherapy is associated with significant and persisting benefits, and remains an appropriate treatment modality in patients with HER2-positive early breast cancer. The significant disease-free survival benefit is maintained at 4 years while the overall survival benefit is no longer significant in intention-to-treat analysis, probably because of the

## *Panel:* Research in context

### Systematic review

The HERA trial was prompted by the results of phase 3 trials that showed the benefit of treatment with trastuzumab in patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer and the subsequent approval of the drug for treatment of metastatic disease. The benefits shown in metastatic disease led to four large randomised trials in patients with HER2-positive early breast cancer,[13,14] of which the HERA trial was the largest. At the time enrolment began, no data were available regarding the effects of adjuvant trastuzumab on HER2-positive breast cancer.

### Interpretation

The first interim analysis of the HERA trial was done in patients receiving chemotherapy plus 1 year of adjuvant trastuzumab versus chemotherapy plus observation after median follow-up of 1 year. The interim analysis showed addition of trastuzumab significantly improved disease-free survival.[9] The demonstrated benefit of trastuzumab prompted a protocol amendment to allow suitable patients from the observation arm to cross over and receive trastuzumab. This was followed by confirmation that 1 year of adjuvant trastuzumab plus chemotherapy significantly improved overall survival.[12] The 4-year follow-up data presented here confirm a persisting disease-free survival benefit in patients initially randomly assigned to 1-year trastuzumab compared with observation although selective crossover is confounding the updated analysis of the HERA results. Other large adjuvant trials have also reported durable disease-free survival benefit of trastuzumab therapy.[13,15,22] These studies and the updated HERA data confirm the benefit of treatment with 1-year trastuzumab plus chemotherapy in patients with HER2-positive early breast cancer. The optimum duration of treatment with trastuzumab is the subject of ongoing studies.

effect of trastuzumab and lapatinib use post-relapse and trastuzumab use before recurrence in the observation group. The extensive selective crossover has attenuated these efficacy findings, with lack of randomisation of crossover patients introducing possible bias. Our exploratory analyses suggest that patients who received delayed administration of trastuzumab, at a median of nearly 2 years after completion of chemotherapy, had a lower risk of an event, but this observation is not based on a randomised comparison. The use of a late anti-HER2 strategy is being prospectively tested in the TEACH trial, with lapatinib as the anti-HER2 drug (NCT 00374322).[25] The data are consistent with the hypothesis that risk of relapse in patients with HER2-positive early breast cancer persists over time and that women might derive further benefits with trastuzumab therapy beyond 1 year. This hypothesis is being explored in the comparison of the 1-year and 2-year trastuzumab groups in the HERA trial.

#### Contributors

LG contributed to the study design, data collection, analysis and interpretation, and wrote the first and final drafts of this report. UD contributed to the data analysis and interpretation and writing of the report. RDG contributed to the design, conduct, analysis, and reporting of the trial in his role as senior statistician. EA and MJE contributed to the study design, data collection, analysis and interpretation, and writing of the manuscript. SM contributed to the collection and review of data. AG contributed to the study design, conduct, and interpretation of the results. MU and RB contributed to the study design, data collection, analysis and interpretation, and writing of the report. IS contributed to the study design and review of the report. JB contributed to the design, conduct, and interpretation of the data. CJ contributed to the study design, data collection, analysis and interpretation. DC was an investigator in the HERA trial, and 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. MM contributed to the conduct of the trial as medical advisor. JLP, AV, CM, AP, and ZS contributed to the data collection. VS contributed to the data collection and interpretation. EV contributed to the data collection, analysis, and interpretation. GS contributed to the data analysis and interpretation. MP contributed to the statistical analysis and interpretation of data. KIP contributed to the writing of the report. MJP-G contributed to the design, conduct, and analysis of the trial as chief investigator and in writing the reports. All authors saw and approved the final version of the report.

#### Conflicts of interest

LG has received payments for membership of advisory boards for Roche. RDG was provided with financial support through Roche's support for the International Breast Cancer Study Group and Breast International Group. IS has received speaker's honoraria from Roche. CJ has received consultancy fees from Roche in relation to the HERA trial, and travel expenses and speaker's honoraria. EA has received consultancy fees from Roche in relation to the HERA trial and speaker's honoraria. MM has received travel expenses from Roche in relation to the HERA trial and speaker's honoraria. CM and EV have received consultancy fees from Roche in relation to the HERA trial, and travel expenses and speaker's honoraria. EV has received consultancy fees and payments for advisory board membership, speaking engagements, and related travel expenses. CM has received consultancy fees, payment for speaking engagements, and related travel expenses. GS's institution received funding from Roche in relation to the HERA study. JP received travel expenses from Roche to attend HERA-related meetings. AV has received research funding and travel expenses from Roche. DC and RB have received research funding from Roche in relation to the HERA trial, honoraria for speaking engagements, and consultancy fees and travel expenses from Roche. MJP-G and JB have received consultancy fees from Roche for work unrelated to this study. KIP has received consultancy fees from Roche in relation to the HERA trial. SM is an employee of F Hoffmann-La Roche and has stock options in the company. The other authors declare that they have no conflicts of interest.

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