11 years' follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer: final analysis of the HERceptin Adjuvant (HERA) trial

HERceptin Adjuvant (HERA) Trial final analysis: 11-year follow up of trastuzumab after adjuvant chemotherapy in HER2-positive early breast cancer

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Summary

Background: Clinical trials have demonstrated that trastuzumab, a recombinant monoclonal antibody against HER-2 receptor, significantly improves overall (OS) and disease-free survival (DFS) in women with HER2-positive (HER2+) early breast cancer, but long-term follow-up is required.

Methods: HERA (BIG 1-01) is an international, multicenter, open label, phase III randomized trial involving 5102 women with HER2+ early breast cancer enrolled between December 2001 and June 2005. After completing all primary therapy, including surgery, chemotherapy and radiotherapy as indicated, patients were randomized to trastuzumab for 1 year, trastuzumab for 2 years, or observation. Primary endpoint is DFS, and analyses are intent-to-treat. After release of positive results in May 2005, 884 (over 50%) of patients assigned to observation selectively crossed over to receive trastuzumab. Hazard ratios (HRs) were estimated from Cox models, and survival curves were estimated by Kaplan-Meier method. Comparison of 2 years versus 1 year of trastuzumab is based on 366-day landmark analyses. This study is registered with ClinicalTrials.gov, number NCT00045032.

Findings: After 11 years of median follow up, random assignment to 1 year of trastuzumab significantly reduced the risk of a DFS event (HR 0·76, 95% CI 0·68–0.·86) and death (HR 0·74, 0·64–0·86) compared with observation. Two years of adjuvant trastuzumab did not improve outcome compared with one year of administration for DFS (HR 1·02, 0·89–1·17). Estimates of 10-year DFS for observation or 1 year or 2 years of trastuzumab were 62·5%, 69·3%, 68·5%, and 12-year OS estimates were 72·9%, 79·4%, 79·5%, respectively. Cardiac toxicity

remained low and occurred mostly during the treatment phase.

Interpretation: One year of adjuvant trastuzumab following chemotherapy for patients with HER2+ early breast cancer significantly improves long-term DFS and OS outcomes with 11 years of median follow up. Two years of trastuzumab had no additional benefit.

Funding: Hoffman La Roche (Roche)

Word count = 298

INTRODUCTION

Fifteen to twenty percent of patients with early breast cancer have tumours that exhibit overexpression and/or amplification of the HER2 receptor/ oncogene, and the use of adjuvant trastuzumab (Herceptin®) is now standard of care for these patients. Four large randomised trials have clearly demonstrated that trastuzumab has a major impact in reducing recurrence and death in patients with this type of early breast cancer. The initial trials compared one year of trastuzumab treatment with a no trastuzumab control.[1–3] Further follow up confirmed a persistent benefit of one year of treatment versus observation.[4–7] The HERA (HERceptin Adjuvant) trial is unique in that it also included randomization of patients to two years of trastuzumab. Demonstration that two years of trastuzumab was not superior to one year of trastuzumab[7] reinforced the use of one year of treatment as the standard of care. Long-term follow up of patients with HER2-positive breast cancer is important to better understand the true impact of this disease, the benefits of trastuzumab, and long-term cardiovascular safety. This paper reports the results of the comparison between observation, one and two years of trastuzumab at 11-years' median follow up within the HERA study.

MATERIALS AND METHODS

Study design

Between December 7, 2001 and June 20, 2005, a total of 5102 patients were randomised (in a 1:1:1 ratio) to one of the 3 arms of the HERA trial as previously reported.[1] Methods used to generate the random allocation sequence, stratification

factors, type of randomization, approval of the protocol by local ethics committees at each hospital, the need for each patient to give signed informed consent, and open label design are described elsewhere.[5] The comparison of the trastuzumab arms versus observation was based on the intent-to-treat (ITT) principle, after excluding three patients with no record of written informed consent (Figure 1 consort diagram). The comparison of 2 years versus 1 year of trastuzumab was based on a 12-month landmark analysis involving the 3105 women who remained alive and disease-free for at least 12 months (366 days) after randomization to one of the two trastuzumab arms.[7] Written informed consent, central laboratory (Kassel, Germany) confirmation of locally assessed HER2-positive disease, and left ventricular ejection fraction (LVEF) ≥ 55% after completion of all chemotherapy with or without radiotherapy (Figure 1) were required. Open-label trastuzumab was administered intravenously using the doses and schedule shown in Figure 1. Adjuvant endocrine therapy for women with steroid hormone receptor positive cancers was administered concomitantly with and after trastuzumab according to local protocols.

Follow-up procedures

All patients adhered to the same schedule of follow-up visits, which required the recording of symptoms, side effects (graded according to the National Cancer Institute Common Toxicity Criteria [NCI-CTC] version 2·0), and findings on clinical examination every three months for the first two years from randomization, with hematologic and chemistry studies performed every six months. These assessments were scheduled to occur every six months for years 3 to 5 and then annually up to year 10. Annual chest radiography was required to year 5 and annual mammography to year 10. Study visits for individual patients continued for 10 years from randomization with full

recording of breast cancer recurrences, contralateral breast cancer and second primaries. Selected adverse events, such as cardiac endpoints, were also collected. For patients who were alive and disease-free at the 10-year visit, the calculation of DFS included the additional follow-up time reported beyond 10 years and deaths reported during the additional follow-up period were counted as DFS events.

Cardiac monitoring and endpoints

Cardiac monitoring in the trastuzumab and the observation arms included clinical assessments and measurements of left ventricular ejection fraction (LVEF) by either echocardiography or MUGA scanning at baseline, months 3, 6, 12, 18, 24, 30, 36, and annually thereafter up to 10 years from randomization. A primary cardiac endpoint was defined as New York Heart Association (NYHA) class III or IV toxicity, confirmed by a cardiologist, and a significant left ventricular ejection fraction (LVEF) drop of at least 10 percentage points from baseline and to an absolute LVEF below 50%, or cardiac death. A secondary cardiac endpoint was defined as asymptomatic (NYHA class I) or mildly symptomatic (NYHA class II) with a significant LVEF drop of at least 10 percentage points below baseline and to an absolute LVEF below 50% confirmed by repeat assessment. An algorithm was defined in the protocol prescribing delay or cessation of trastuzumab in response to cardiac endpoints.

Endpoints and statistical considerations

This analysis was a pre-planned final efficacy analysis of the HERA trial. The primary endpoint was disease-free survival (DFS) as described previously,[1] with events ending DFS almost identical to those used to define invasive disease free survival

(IDFS) using STEEP criteria.[8] Secondary endpoints included overall survival (OS), sites of first relapse, competing risk cumulative incidence analysis of breast cancer and non-breast cancer DFS events, and prospectively planned efficacy analyses by local assessment of steroid hormone receptor status of the primary tumour.

Safety, particularly cardiac safety, was also a secondary endpoint. Safety populations were generally defined according to randomised assignment, except that 20 patients assigned to 1 year and 25 patients assigned to 2 years of trastuzumab who never received trastuzumab were allocated to the observation safety population. Two additional patients randomized to 2 years of trastuzumab who initially refused trastuzumab but chose to receive trastuzumab after the release of the study results are included in the observation safety population until the time they started trastuzumab. Adverse events were considered from the time of randomization. Adverse events, including cardiac endpoints, recorded after crossover to trastuzumab of patients in the observation arm were excluded.

The updated comparison of 1 year of trastuzumab versus observation was based on 1702 and 1697 patients enrolled in the two arms, respectively, using an intention-to-treat analysis from the time of randomization. A total of 884 (52·1%) of the 1697 patients in the observation arm selectively crossed over to receive trastuzumab after the release of the initial results of this and other trials in 2005,[1,2] of whom 477 (54.0%) had hormone receptor positive disease and 407 (46.0%) had hormone receptor negative disease (data not shown). As previously described,[5] the selective crossover improved outcomes for the observation arm in the intention-to-treat analysis, resulting

in an underestimation of the true trastuzumab treatment effect had there been no selective crossover.

Log-rank tests for time-to-event endpoints provided two-sided P values. Kaplan–Meier curves are presented.[9] Cox proportional hazards modelling was used to estimate unadjusted hazard ratios and 95 percent confidence intervals.[10] The cumulative incidence of cardiac endpoints based on competing risks was calculated.[11] Exploratory Cox modelling was performed to examine interactions between treatment assignment, hormone receptor status, and time on study. Time-varying covariate Cox modelling[11] was performed to explore the effect of selective crossover on the risk of a DFS event in the no trastuzumab control group.

Updated trastuzumab comparison

The comparison of 2 years versus 1 year of trastuzumab was based on a 12-month landmark analysis involving the 3105 women who remained alive and disease-free for at least 12 months (366 days) after randomization to one of the two trastuzumab arms.

Role of the sponsor

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, 91 independent centres, and the pharmaceutical sponsor, Roche, all of which were represented in the Steering Committee of the HERA trial. The study was designed by members of the Steering Committee. The database was maintained at the Breast European Adjuvant Study Team (BrEAST) Data Centre, Brussels, Belgium. For the

final analysis, the HERA Executive Committee, on behalf of the HERA Steering Committee, was responsible for the decision to publish and for the content of the manuscript. The pharmaceutical sponsor provided the drug, some site monitoring and financial support.

RESULTS

Patient population

The cohorts for comparison were well balanced with respect to demographics and baseline disease characteristics including tumour size, nodal and hormone receptor status (Table 1). Overall 2571 (50·4%) of the patients had hormone receptor positive disease and 2528 (49·6%) had hormone receptor negative disease by local laboratory determination of hormone receptors. A total of 2370 (92·2%) of the hormone receptor positive cases received adjuvant endocrine therapy. Most patients received chemotherapy only postoperatively but in 563 (11·0%) preoperative neoadjuvant chemotherapy had been administered. Chemotherapy included an anthracycline for 4797 (94·1%) of the patients, and an anthracycline and taxane for 1328 (26·0%) of the patients. Patients with node negative disease were eligible for enrolment if the pathological tumour size was larger than 1 cm, and 1646 (32·3%) of the patients had node-negative disease. Overall 2642 (51·8%) of the patients were 49 years of age or younger at the time of study entry. Patients in the HERA study started trastuzumab at a median of 8·4 months (interquartile range [IQR] 7·1 – 9·6 months) after initial diagnosis of breast cancer and a median of 89 days (IQR 46-112 days) after completing all chemotherapy.

Comparison of trastuzumab versus observation

In this final report, results for 1 year of trastuzumab (18 cycles median of q3weekly) versus observation were based on 1113 DFS events [1103 (99·1%) satisfied the STEEP criteria for IDFS events] and 725 of the patients had died (an OS event). A total of 884 (52·1%) of the observation arm patients received trastuzumab before a DFS event due to selective crossover after publication of the initial trial results. Despite this selective crossover, using an ITT analysis, the hazard ratio after 11 years of median follow up was 0·76 (95% CI 0·68-0·86) for 1-year trastuzumab vs observation. The hazard ratio for 2-years trastuzumab (35 cycles median of q3 weekly) vs observation was similar, 0·77 (95% CI 0·69-0·87). The 10-year DFS rate was 62·5%, 69·3% and 68·5% in the observation, 1-year trastuzmab and 2-years trastuzumab arms, respectively (Figure 2, Panel A). This corresponded to an absolute benefit of 6·8% and 6·0% in DFS at 10 years for 1-year trastuzumab and 2-years trastuzumab compared to observation, respectively. Of note in interpreting the ITT analysis is the fact that about half of the follow-up time in the observation arm was accrued after selective crossover to trastuzumab. The annualized hazard rates for disease-free survival over time are shown in Figure S1 (appendix). The exploratory time-varying covariate Cox model showed that selective crossover was associated with a reduction in risk of a DFS event in the observation arm (hazard ratio 0·79, 95% CI 0·64-0·98) (Table S3; appendix). Selective crossover was associated with a numerically lower impact for the hormone receptor positive cohort (0·92, CI 0·70-1·22) than for the hormone receptor negative cohort (0·69, CI 0·53-0·91) (Table S3; appendix); (interaction p-value=0·10) (Table S2; appendix).

In the hormone receptor positive cohort, the hazard ratio (1-year trastuzumab vs observation) was 0·80 (95% CI 0·68-0·96) and the absolute benefit in 10-year DFS

rate was 5·6%. The 10-year DFS rates were 65·9%, 71·5% and 69·6% in the observation, 1-year trastuzumab and 2-years trastuzmab arms, respectively (Figure 2, Panel B). In the hormone receptor negative cohort, the 10-year DFS rates were lower; 59·1%, 67·1% and 67·3% for the observation, 1-year trastuzumab and 2-years trastuzumab arms, respectively. The hazard ratio for 1-year trastuzumab vs observation was 0·73 (95% CI 0·62-0·85) and the absolute benefit in 10-year DFS rate was 8·0% (Figure 2, Panel C). Exploratory Cox models comparing trastuzumab (both 1- and 2-years combined) versus observation indicated that time since randomization was significantly associated with treatment effect for both hormone receptor positive and negative populations. Hazard ratios for early DFS events (up to 24 months from randomization) were 0·63 (CI 0·52-0·77) for hormone receptor positive and 0·59 (CI 0·50-0·70) for hormone receptor negative cohorts (Table S5; appendix). Corresponding hazard ratios for later DFS events (24 months or more after randomization) were 0·98 (CI 0·82-1·16) and 0·91 (0·76-1·09), respectively (Table S5; appendix).

Subgroup analyses of DFS by nodal status are shown in Table S6 (appendix). As expected, DFS was worse for patients with higher numbers of positive axillary lymph nodes. In the 1-year trastuzumab arm, the 10-year DFS rates were 80·1% for the node negative cohort, 74·5% for the 1-3 positive nodes cohort, and 54·5% for the ≥ 4 positive nodes cohort. The hazard ratios (1-year trastuzumab vs observation) were 0·78, 0·64 and 0·82 in these cohorts, respectively.

Table 2 shows the site of first DFS event. The cumulative incidence curves of the competing risk of a DFS event related to breast cancer and of a DFS event not related to breast cancer are shown in Figure 2 (Panels D, E and F). A lower numerical cumulative incidence of DFS events related to breast cancer was seen in the

trastuzumab arms compared to the observation arm for both the hormone receptor positive and negative cohorts. The cumulative incidence of breast cancer-related DFS events was numerically lower in the hormone receptor positive cohort, and with a smaller absolute decrease in the trastuzumab arms, as compared with the hormone receptor negative cohort. No numerical decrease in the incidence of non-breast cancer related DFS events was seen in either the hormone receptor positive or negative cohorts. While clinical benefit of trastuzumab was seen in both the hormone receptor positive and hormone receptor negative cohorts, the timing and rate of DFS events appears different between these cohorts (Figure 2, Panels E-F).

As with DFS, the results for OS also demonstrated a robust and persistent improvement despite the impact of selective crossover (Figure 4, Panel D). The hazard ratio (1-year trastuzumab versus observation) for overall survival at 11 years of median follow up was 0·74 (95% CI 0·64-0·86). The 12-year OS rates were 72·9%, 79·4% and 79·5% in the observation, 1-year trastuzumab and 2-years trastuzumab arms, respectively. The absolute benefit in 12-year OS was 6·5% and 6·6% for 1-year trastuzumab and 2-years trastuzumab, respectively (Figure S3, Panel A; appendix).

Considering OS in the hormone receptor positive cohort, the hazard ratio (1-year trastuzumab vs observation) was 0·81 (95% CI 0·65-1·00). The 12-year OS rates were 76·2%, 80·9% and 80·5% in the observation, 1-year trastuzumab and 2-years trastuzumab arms, respectively (Figure S3, Panel B). In the hormone receptor negative cohort, the 12-year OS rates were lower; 69·6%, 77·9% and 78·6% for the observation, 1-year trastuzumab and 2-years trastuzumab arms, respectively. The hazard ratio for 1-year trastuzumab vs observation was 0·70 (95% CI 0·57-0·85) (Figure S3, Panel C).

Safety

No new safety concerns have emerged since previous reports.[5,7] More patients had at least one grade 3 or 4 adverse event in the trastuzumab groups than the observation group (Table S7; appendix). Primary cardiac endpoints were very rare in this study, which introduced trastuzumab after completing all chemotherapy and radiation therapy and required a post chemotherapy LVEF ≥ 55 prior to enrolment. There was no significant difference in the occurrence of primary cardiac endpoints between the two trastuzumab arms, although the rates were higher than in the observation arm (Table S7; Figure 3, Panel A). Secondary cardiac endpoints occurred more frequently in the 2-years trastuzumab arm than in the 1-year trastuzumab arm, largely because the event rate observed in both arms during the first year continued during the second year only in the 2-years trastuzumab arm (Figure 3). In both trastuzumab arms, there were few cardiac endpoints beyond the completion of trastuzumab treatment. There was no evidence of a noticeable number of cardiac endpoints occurring a long time (approximately 10 years) after randomization (Figure 3).

Update of Trastuzumab Duration Comparison

Compliance with randomised assignment of trastuzumab duration was generally good.[7] The update of the landmark analysis comparison of 2 years versus 1 year of trastuzumab was based on 814 DFS events. There was no evidence of a long-term benefit of 2 years compared to 1 year of trastuzumab when administered as sequential treatment following chemotherapy, with a hazard ratio for DFS of 1·02 (95% CI 0·89 – 1·17) (Figure S5, Panel A). The short-term separation in the DFS curves in the hormone receptor negative cohort was not significant. Here, the long-term hazard ratio

was 0·94 (95% CI 0·77 – 1·14) (Figure S5, Panel C). In the hormone receptor positive cohort, the hazard ratio was 1·10 (95% CI 0·91 – 1·34) (Figure S5, Panel B).

DISCUSSION

After 11 years of median follow-up, it remains clear that the use of 1 year of adjuvant trastuzumab significantly improves disease outcomes when given in addition to standard of care, including chemotherapy, in patients with HER2-positive early breast cancer. The relative risk of a DFS event is reduced by 24%, conferring an absolute benefit of 6.8% improvement in 10-year DFS in those women randomised to 1-year trastuzumab as compared to those in the observation arm. Further, a 6.5% absolute gain was found in overall survival at 12 years. As previously noted,[5] since just over half the patients in the observation arm crossed-over to receive trastuzumab after release of the initial results of this trial, these estimates of absolute benefit are likely to be underestimates of the true benefit for patients. In fact, in the current analysis, selective crossover was associated with a 21% relative reduction in the risk of a DFS event in the observation arm, thus clearly attenuating the trastuzumab effect estimated by the ITT analysis. Furthermore, trastuzumab treatment effects were significantly greater during the first 24 months since randomization compared with later during follow up, a finding that may be partially attributable to crossover.

Subgroup analysis by tumour hormone receptor status confirms two important observations. Firstly, despite overexpression of the HER2 oncogene, hormone receptor status remains a powerful determinant of disease outcome, with more recurrences and deaths in the women with hormone receptor negative disease even after 11 years' median follow-up. Furthermore, the data suggest that the timing of

recurrences is different, with a higher initial rate of DFS events in the patients with hormone receptor-negative disease, although events still accumulate out to 10 years in both groups. Table 2 reports the sites of first recurrence, where it is clear that all sites of recurrence are slightly more common in patients with hormone receptor-negative, HER2-positive breast cancer, with the exception of skeletal distant recurrence, in keeping with what has been previously seen in non HER2-positive disease. Secondly, there is no evidence that the efficacy of trastuzumab is different according to the hormone receptor status of the primary tumour. Numerically, the hazard ratio was smaller in those women with hormone receptor-positive disease (0·80 vs 0·73 for 1-year trastuzumab vs observation), but the difference is not significant and could be affected by the higher percent of hormone receptor-positive cases who could cross over due to lower risk of early relapses. Benefit is also seen in overall survival in both hormone receptor groups, where the corresponding hazard ratios for 1-year trastuzumab vs observation were 0·81 for hormone receptor-positive and 0·70 for hormone receptor-negative cohorts, respectively.

In earlier reports, there was evidence of progressively smaller apparent benefits of one year of trastuzumab in intention-to-treat analyses previously reported at 2-year and 4-years' median follow up.[5] The DFS hazard ratio for 1-year trastuzumab versus observation has however been stable since 4-years median follow up, 0·76 (Figure 4, Panel A). The results demonstrate a robust and persistent improvement in DFS despite the impact of selective crossover (Figure 4). Interestingly, despite the increased tendency for patients with hormone receptor-positive disease to have relapsed later, the estimated hazard ratios for DFS benefit stabilised at around 4 years'

follow-up in both the hormone receptor cohorts, suggesting a profound and permanent effect of one year of trastuzumab on micrometastatic disease.

Considering overall survival in the women with hormone receptor-negative and hormone receptor-positive tumours separately, in all analyses of 1-year trastuzumab vs observation there were fewer deaths in those women with hormone receptor-positive disease than hormone receptor-negative disease. Approximately half of the women enrolled into the HERA trial had hormone receptor-positive disease, whereas the true proportion in an incident breast cancer population may be nearer 60%.[12] Thus this difference in timing of events, particularly for overall survival, means that interpretation of more recent clinical trials of adjuvant therapy in this patient population may require more cautious analysis. If the true benefit in the majority population of hormone receptor-positive tumours takes longer to appear, earlier analyses of overall survival could result in false negative conclusions.

This manuscript also includes an updated analysis of a unique feature of the HERA trial, namely addressing the duration question by randomising 1/3 of the patients to a longer, 2-year duration of trastuzumab. The earlier report found no advantage for the longer therapy, and this is confirmed with this more mature analysis. This has real clinical relevance – there is no evidence that subjecting women to longer therapy with trastuzumab is the way to further reduce the risk of relapse and death from HER2-positive early breast cancer. Data from several studies, including those in the neo-adjuvant and metastatic disease settings[12-15] all indicate that greater anti-tumour activity is seen when combining two anti-HER2 agents, although the first report from the ALTTO study of the small molecule HER2 inhibitor lapatinib combined with one year of trastuzumab[12], did not find a clinically meaningful benefit. The only other study

reporting outcomes for longer than one year's duration of anti-HER2 therapy was the ExteNET study[16]. That study tested the benefit of one year of a small molecule pan-HER2 tyrosine kinase inhibitor after one year of trastuzumab, and the design was altered during the study to report events at 2 years in all patients and thus does not have long-term outcome data comparable to that reported here for HERA.

This updated analysis of the HERA study again indicates that there may be a temporary benefit in DFS in those patients with hormone receptor-negative disease randomised to 2 years of trastuzumab compared to 1 year of trastuzumab. This may well be the play of chance, but with other emerging data it does pose the hypothesis that there may be other ways to enhance the efficacy of this agent in the adjuvant setting. For women with hormone receptor-positive tumours, even when HER2 overexpressing, at least 5 years of adjuvant endocrine therapy is standard of care. This study and others[3,6] confirm that despite this prolonged anti-tumour therapy, trastuzumab gives clear additional benefit if given for one year, but once that is stopped, the tumours are generally still subjected to active anti-cancer, endocrine therapy. By contrast, for those patients whose tumours are hormone receptor-negative, once the trastuzumab is stopped and systemic levels fall, there is no anti-tumour therapy given. As we now realise that part of the efficacy of trastuzumab may be due to its ability to induce an immunologically mediated anti-tumour effect[17], this raises the possibility that concurrent modulation of the immune system, rather than further treatment with an anti-HER2 agent, could be of benefit. One might further conjecture that the transient short-term benefit from additional trastuzumab beyond 1 year is seen because the prolonged higher antibody levels maintain that immune recruitment, but to an insufficient degree to effectively eradicate microscopic disease.

In patients with hormone receptor-positive disease, the prolonged anti-endocrine therapy may mask the signal of any additional temporary benefit from immune enhancement. This would lead to the hypothesis that addition of agents that enhance the immune anti-tumoural effect during the first year of therapy could be of real benefit if given in conjunction with trastuzumab acting as the “recruiter” of that immune response.

A further important finding from this 11-year analysis is the safety of adjuvant trastuzumab. The unique feature of HERA is that serial LVEF assessment up to 10 years was performed in all patients, which provides more complete cardiac information compared to the other adjuvant trastuzumab trials. No new safety signals have emerged despite the prolonged follow-up, and, in particular, no signal of late cardiac problems, despite the aging by one decade of the cohort in follow up subjecting them to an increased risk of age related cardiac morbidity. For those women randomised to the 2-year trastuzumab arm, there are more low-level cardiac endpoints seen during treatment, which these patients will have experienced despite the lack of additional benefit compared with 1-year trastuzumab. However, it is reassuring that the frequency during the second year remained similar to that observed during the first year, with few cardiac endpoints reported beyond 2 years, and the evidence that those that do occur are mostly reversible.[18]

The selective crossover of just over half of the control arm patients is a clear limitation of this later intention-to-treat analysis of the HERA trial, though it is likely to provide an underestimate of the long-term efficacy of adjuvant trastuzumab. The lack of access

to all the primary tumour samples also precludes exploratory translational analyses that could allow better understanding of the biology of those tumours that relapse despite the use of adjuvant trastuzumab, and thus facilitate development of additional therapeutic approaches that could be beneficial.

In conclusion, long-term follow-up of practice-changing clinical trials, such as the HERA trial, is essential to inform doctors and patients about the full range of benefits and burdens associated with new widely-adopted treatments. This 11-year median follow up analysis confirms a 24% relative reduction in risk of a DFS event, and a 26% relative reduction in risk of death, with the addition of one year of adjuvant trastuzumab in women with HER2-positive early breast cancer. There is no evidence of additional benefit from a second year of trastuzumab, but some evidence of additional cardiac toxicity with longer duration treatment. These results have been stable over the last several years of additional follow up. The benefits of one year of adjuvant trastuzumab are substantial for both individual patients and breast cancer populations, and indeed may even be underestimated due to the crossover of half of the observation arm. The benefits are seen irrespective of node status and tumour steroid hormone receptor status, although the absolute benefits for an individual do depend on their underlying risk of recurrence after other standard therapies. The HERA study therefore confirms that one year of trastuzumab remains an important, and curative, part of the standard of care for women with HER2-positive early breast cancer.

Word count = 4325 m/s only : 4725 including acknowledgements & research in context.

Acknowledgements

This study was funded by F Hoffmann-La Roche (Roche). We thank the women who participated in the study; the Breast European Adjuvant Study Team Data Centre; the Frontier Science Team; the Breast International Group Secretariat; the HERA Steering Committee; the Independent Data Monitoring Committee; the Cardiac Advisory Board; the Pathology Laboratory, Kassel, Germany; F Hoffmann-La Roche; and the doctors and nurses who participated in HERA. All participating cooperative groups and centres are acknowledged in the text and in the appendix of reference 1.

Panel: Research in context

Systematic review

We searched PubMed for randomised clinical trials published in English between Jan 1, 2000, and March 1, 2013, assessing long-term outcomes (> 5 years follow-up) from randomised trials of systemic therapy in patients with early breast cancer confirmed as HER2 positive, using the search terms “adjuvant”, “breast”, “randomised” and “HER2”. There was no data in the literature providing 10 or more years’ follow-up from the use of adjuvant trastuzumab within a randomised trial.

Added value of this study:

To our knowledge, this report of the 11-year follow up of the HERA trial provides the longest survival data of any trial that assessed the addition of anti-HER2 therapy to standard treatment for HER2-positive early breast cancer. It provides long-term patient outcome data to support the use of 1 year of adjuvant trastuzumab in this patient population, with evidence that those patients randomised to receive trastuzumab have sustained relative reductions in recurrence and breast-cancer deaths, with the

reassurance that the rate of serious toxicity is not increasing over time. It also provides no evidence of benefit of longer duration of trastuzumab, nor that there is any group studied in the HERA trial who did not derive long-term benefits.

Implications of all the available evidence:

Patients with early HER2-positive early breast cancer who meet the criteria for the HERA trial (or the other studies reported elsewhere), including the cardiac disease criteria, should be offered one year of adjuvant trastuzumab as part of standard of care. Patients can be reassured that there are benefits in terms of better disease-free and overall survival that are sustained to at least ten years after diagnosis, with no evidence of significant differential benefit by disease characteristics such as nodal status or tumour hormone receptor status. In addition there is no evidence of late emergent side effects, including no evidence of more cardiac endpoints emerging ten years after treatment.

Contributions:

DC contributed to trial management, literature search, data analysis and interpretation, manuscript writing and approval of the final manuscript. MJP-G was Principal Investigator and trial management, literature search, data analysis and interpretation, manuscript writing and approval of the final manuscript. RDG contributed to the study design, data analysis, data interpretation, and writing of the report. MP contributed to data analysis and interpretation, manuscript writing and approval of the final analysis.AG contributed to Trial design, data analysis and interpretation, manuscript writing and approval of the final manuscript. EdA

contributed to trial management, data assembly, data interpretation, manuscript review and final approval. GC contributed to data interpretation, manuscript writing and approval of the final manuscript. MU contributed to Study design, data collection, data analysis, data interpretation, writing. IS contributed to trial management, literature search, data analysis and interpretation, manuscript writing and approval of the final manuscript. LG contributed to Trial management, literature search, data analysis and interpretation, manuscript writing and approval of the final manuscript. JB contributed to the study design, study conduct and coordination, data interpretation, and writing and approval of the mansucript. NAS contributed to Trial management, manuscript review and approval. SL contributed to Trial management, literature search, data analysis and interpretation, writing of the manuscript and final approval. EM contributed to study design, data collection, trial management, article review, steering committee and executive committee membership. BL-J contributed to the Trial design, data analysis and interpretation & manuscript review. RB contributed to tudy Design, Study Conduct (Executive Committee and Steering Committee), data interpretation, writing and review of manuscript. MD contributed to trial management, data analysis and interpretation, approval of the final manuscript. CJ Trial design, trial management, literature research, data analysis and interpretation, manuscript writing and approval of the final manuscript.

Declaration of interests:

NAS reports grants and other from F. Hoffmann-La Roche Ltd., outside the submitted work; and employment relationship. RB reports personal fees from Roche, outside the submitted work. DC reports grants and other from Novartis, other from BIOENSIS, outside the submitted work; EDA reports grants and other from Roche. MD reports grants from Roche/Genetech, during the conduct of the study; grants and

personal fees from Roche/Genetech, outside the submitted work. RG reports grants as support for his academic salary from Breast International Group (BIG) and Roche during the conduct of the study; and grants as support for his academic salary from GlaxoSmithKline, Pfizer, Merck, Celegene, and Novartis, outside the submitted work; LG reports grants and other from Novartis, outside the submitted work. SL reports personal fees from Hoffmann La Roche Ltd., during the conduct of the study; personal fees from Hoffmann La Roche Ltd., outside the submitted work. BLJ reports he was a member of a Scientific Advisory Board pertaining to biosimilars of Herceptin within the past year. EMF reports other from Frontier Science (Scotland) Ltd, during the conduct of the study; other from Novartis, other from AstraZeneca, other from ROCHE, other from GSK, outside the submitted work. MP reports personal fees from Roche outside the submitted work, MPR reports that her institution received funding from Roche to conduct the study, IS reports grants and other from Novartis, outside the submitted work.

JB, GC, AG, CJ & MU reports no conflicts of interest.

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Table 1. Demographic and Baseline Disease Characteristics of the Patients (Intent-to-Treat Population)

Characteristic	Observation (N=1697)	1 Year of Trastuzumab (N=1702)	2 Years of Trastuzumab (N=1700)
Age at study entry – no. (%)			
< 35 years	126 (7.4%)	128 (7.5%)	124 (7.3%)
35 – 49 years	752 (44.3%)	756 (44.4%)	756 (44.5%)
50 – 59 years	546 (32.2%)	546 (32.1%)	547 (32.2%)
>= 60 years	273 (16.1%)	272 (16.0%)	273 (16.1%)
Previous (neo)adjuvant chemotherapy - no. (%)			
No Anthracycline	99 (5.8%)	101 (5.9%)	102 (6.0%)
Anthracycline but no taxane	1158 (68.2%)	1153 (67.7%)	1158 (68.1%)
Anthracycline + taxane	440 (25.9%)	448 (26.3%)	440 (25.9%)
Menopausal status – no. (%)[1]			
Premenopausal	234 (13.8%)	258 (15.2%)	225 (13.2%)
Uncertain	691 (40.7%)	684 (40.2%)	686 (40.4%)
Postmenopausal	770 (45.4%)	760 (44.7%)	789 (46.4%)
Pathological tumor size – no. (%)			
Not assessed (neoadjuvant chemotherapy)	178 (10.5%)	194 (11.4%)	191 (11.2%)
0-2 cm	683 (40.2%)	668 (39.2%)	652 (38.4%)
>2-5 cm	724 (42.7%)	760 (44.7%)	741 (43.6%)
>5 cm	96 (5.7%)	71 (4.2%)	106 (6.2%)
Missing size	16 (0.9%)	9 (0.5%)	10 (0.6%)
Nodal status – no. (%)[2]			
Not assessed (neoadjuvant chemotherapy)	178 (10.5%)	194 (11.4%)	191 (11.2%)
Negative	555 (32.7%)	543 (31.9%)	548 (32.2%)
1-3 Positive nodes	490 (28.9%)	486 (28.6%)	488 (28.7%)
≥ 4 Positive nodes	473 (27.9%)	479 (28.1%)	473 (27.8%)
Hormone Receptor Status (Local) – no. (%)[3]			
Positive (ER and/or PgR positive)	855 (50.4%)	859 (50.5%)	857 (50.4%)
Negative (ER and PgR negative) [4]	842 (49.6%)	843 (49.5%)	843 (49.6%)

Footnotes for Table 1:

[1] Menopausal status at randomization

[2] One patient with missing nodal status in the observation arm

[3] One patients in the 1 year trastuzumab arm with unknown estrogen status and progesterone receptor-positive status

[4] This category also includes patients with ER negative and PgR unknown

Table 2: Site of first disease-free survival event

Table 2A. Site of First Disease-Free Survival Event (ITT population)[1]			
Variable	**Observation (N=1697)**	**1 Year of Trastuzumab (N=1702)**	**2 Years of Trastuzumab (N=1700)**
Number of patients with event	608 (35.8%)	505 (29.7%)	518 (30.5%)
Local recurrence	98 (5.8%)	80 (4.7%)	78 (4.6%)
Regional recurrence	29 (1.7%)	18 (1.1%)	24 (1.4%)
Distant recurrence	383 (22.6%)	305 (17.9%)	291 (17.1%)
Central nervous system	36 (2.1%)	45 (2.6%)	32 (1.9%)
Visceral site	182 (10.7%)	127 (7.5%)	134 (7.9%)
Skeletal	90 (5.3%)	84 (4.9%)	78 (4.6%)
Soft tissue	75 (4.4%)	49 (2.9%)	47 (2.8%)
Contralateral breast cancer[2]	38 (2.2%)	42 (2.5%)	45 (2.6%)
Second (primary) malignancy[3]	40 (2.4%)	47 (2.8%)	60 (3.5%)
Death, no evidence of disease	20 (1.2%)	13 (0.8%)	20 (1.2%)

[1]In cases with multiple simultaneous sites of first event, a hierarchy assigned the event to the first applicable category in order: distant recurrence, regional recurrence, local recurrence, contralateral breast cancer, and second (primary) malignancy.

In cases with multiple simultaneous sites of distant recurrence as first event, a hierarchy assigned the type of distant recurrence in order: central nervous system, visceral, skeletal, soft tissue.

[2]Includes contralateral invasive disease and/or DCIS. There are 4 DFS events of contralateral DCIS which are not IDFS events under the STEEP definition.

[3]Includes second (non-breast) malignancies, invasive ipsilateral tumors of a different type from the primary breast cancer and ipsilateral DCIS events. The category does not include contralateral breast cancer of any kind. There are 8 DFS events of an ipsilateral tumour of a different type from the primary breast cancer which are not IDFS events under the STEEP definition

Table 2B. Site of First Disease-Free Survival Event (hormone receptor positive cohort)[1]

Variable	Observation (N=855)	1 Year of Trastuzumab (N=859)	2 Years of Trastuzumab (N=857)
Number of patients with event	277 (32.4%)	236 (27.5%)	252 (29.4%)
Local recurrence	42 (4.9%)	35 (4.1%)	38 (4.4%)
Regional recurrence	13 (1.5%)	7 (0.8%)	16 (1.9%)
Distant recurrence	177 (20.7%)	156 (18.2%)	137 (16.0%)
Central nervous system	11 (1.3%)	21 (2.4%)	15 (1.8%)
Visceral site	76 (8.9%)	56 (6.5%)	50 (5.8%)
Skeletal	57 (6.7%)	54 (6.3%)	49 (5.7%)
Soft tissue	33 (3.9%)	25 (2.9%)	23 (2.7%)
Contralateral breast cancer[2]	14 (1.6%)	14 (1.6%)	21 (2.5%)
Second (primary) malignancy[3]	21 (2.5%)	18 (2.1%)	27 (3.2%)
Death, no evidence of disease	10 (1.2%)	6 (0.7%)	13 (1.5%)

[1]In cases with multiple simultaneous sites of first event, a hierarchy assigned the event to the first applicable category in order: distant recurrence, regional recurrence, local recurrence, contralateral breast cancer, and second (primary) malignancy.

In cases with multiple simultaneous sites of distant recurrence as first event, a hierarchy assigned the type of distant recurrence in order: central nervous system, visceral, skeletal, soft tissue.

[2]Includes contralateral invasive disease and/or DCIS. There are 2 DFS events of contralateral DCIS which are not IDFS events under the STEEP definition.

[3]Includes second (non-breast) malignancies, invasive ipsilateral tumors of a different type from the primary breast cancer and ipsilateral DCIS events. The category does not include contralateral breast cancer of any kind. There are 3 DFS events of an ipsilateral tumour of a different type from the primary breast cancer which are not IDFS events under the STEEP definition.

Table 2C. Site of First Disease-Free Survival Event (hormone receptor negative cohort)[1]

Variable	Observation (N=842)	1 Year of Trastuzumab (N=843)	2 Years of Trastuzumab (N=843)
Number of patients with event	331 (39.3%)	269 (31.9%)	266 (31.6%)
Local recurrence	56 (6.7%)	45 (5.3%)	40 (4.7%)
Regional recurrence	16 (1.9%)	11 (1.3%)	8 (0.9%)
Distant recurrence	206 (24.5%)	149 (17.7%)	154 (18.3%)
Central nervous system	25 (3.0%)	24 (2.8%)	17 (2.0%)
Visceral site	106 (12.6%)	71 (8.4%)	84 (10.0%)
Skeletal	33 (3.9%)	30 (3.6%)	29 (3.4%)
Soft tissue	42 (5.0%)	24 (2.8%)	24 (2.8%)
Contralateral breast cancer[2]	24 (2.9%)	28 (3.3%)	24 (2.8%)
Second (primary) malignancy[3]	19 (2.3%)	29 (3.4%)	33 (3.9%)
Death, no evidence of disease	10 (1.2%)	7 (0.8%)	7 (0.8%)

[1]In cases with multiple simultaneous sites of first event, a hierarchy assigned the event to the first applicable category in order: distant recurrence, regional recurrence, local recurrence, contralateral breast cancer, and second (primary) malignancy.

In cases with multiple simultaneous sites of distant recurrence as first event, a hierarchy assigned the type of distant recurrence in order: central nervous system, visceral, skeletal, soft tissue.

[2]Includes contralateral invasive disease and/or DCIS. There are 2 DFS events of contralateral DCIS which are not IDFS events under the STEEP definition

[3]Includes second (non-breast) malignancies, invasive ipsilateral tumors of a different type from the primary breast cancer and ipsilateral DCIS events. The category does not include contralateral breast cancer of any kind. There are 5 DFS events of an ipsilateral tumour of a different type from the primary breast cancer which are not IDFS events under the STEEP definition.

Figure Legends

(see separate files for figures 1, 2, 3, 4)

Figure 1. CONSORT Diagram of the HERA Trial.

Figure 2. Kaplan-Meier and Cumulative Incidence Plots for Disease-Free Survival.

Kaplan-Meier plots of disease-free survival over time are shown for the entire ITT population (Panel A), for patients with hormone receptor positive disease (Panel B) and for patients with hormone receptor negative disease (Panel C). Cumulative incidence plots for breast cancer and non-breast cancer competing risks are shown for the entire ITT population (Panel D), for the hormone receptor positive cohort (Panel E) and the hormone receptor negative cohort (Panel F).

Figure 3. Cumulative Incidence of Cardiac End Points.

Competing risk analysis showing the cumulative incidence of cardiac end points with disease-free survival events considered as competing risks. Primary (severely symptomatic) cardiac endpoint (Panel A). Both primary and secondary cardiac endpoints (Panel B).

Figure 4. Hazard Ratios and Confidence Intervals Comparing 1 Year Trastuzumab versus Observation (Intention-to-Treat).

Disease-free survival for the entire ITT population (Panel A), for patients with hormone receptor positive disease (Panel B) and for patients with hormone receptor negative disease (Panel C). Overall survival for the entire ITT population (Panel D), for the hormone receptor positive cohort (Panel E) and for the hormone receptor negative cohort (Panel F).

Extended from Goldhirsch et al. (2013). These intention-to-treat analyses are influenced by selective crossover of 884 (52%) of patients in the observation arm who received trastuzumab after the first results were released in 2005. The numbers in parentheses show the percent of follow up time in the intention-to-treat analysis that was accrued after selective crossover for patients assigned to the observation arm.