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

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Summary

Background Clinical trials have shown that trastuzumab, a recombinant monoclonal antibody against HER2 receptor, significantly improves overall survival and disease-free survival in women with HER2-positive early breast cancer, but long-term follow-up data are needed. We report the results of comparing observation with two durations of trastuzumab treatment at a median follow-up of 11 years, for patients enrolled in the HERA (HERceptin Adjuvant) trial.

Methods HERA (BIG 1-01) is an international, multicentre, open-label, phase 3 randomised trial of 5102 women with HER2-positive early breast cancer, who were enrolled from hospitals in 39 countries between Dec 7, 2001, and June 20, 2005. After completion of all primary therapy (including, surgery, chemotherapy, and radiotherapy as indicated), patients were randomly assigned (1:1:1) to receive trastuzumab for 1 year (once at 8 mg/kg of bodyweight intravenously, then 6 mg/kg once every 3 weeks) or for 2 years (with the same dose schedule), or to the observation group. Primary endpoint is disease-free survival, and analyses are in the intention-to-treat population. Hazard ratios (HRs) were estimated from Cox models, and survival curves were estimated by the 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 (NCT00045032).

Findings Of the 5102 women randomly assigned in the HERA trial, three patients had no evidence of having provided written informed consent to participate. We followed up the intention-to-treat population of 5099 patients (1697 in observation, 1702 in 1-year trastuzumab, and 1700 in 2-years trastuzumab groups). After a median follow-up of 11 years (IQR 10·09–11·53), random assignment to 1 year of trastuzumab significantly reduced the risk of a disease-free survival event (HR 0·76, 95% CI 0·68–0·86) and death (0·74, 0·64–0·86) compared with observation. 2 years of adjuvant trastuzumab did not improve disease free-survival outcomes compared with 1 year of this drug (HR 1·02, 95% CI 0·89–1·17). Estimates of 10-year disease-free survival were 63% for observation, 69% for 1 year of trastuzumab, and 69% for 2 years of trastuzumab. 884 (52%) patients assigned to the observation group selectively crossed over to receive trastuzumab. Cardiac toxicity remained low in all groups and occurred mostly during the treatment phase. The incidence of secondary cardiac endpoints was 122 (7·3%) in the 2-years trastuzumab group, 74 (4·4%) in the 1-year trastuzumab group, and 15 (0·9%) in the observation group.

Interpretation 1 year of adjuvant trastuzumab after chemotherapy for patients with HER2-positive early breast cancer significantly improves long-term disease-free survival, compared with observation. 2 years of trastuzumab had no additional benefit.

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Introduction

15–20% of patients with early breast cancer have tumours that exhibit overexpression, amplification, or both, of the HER2 receptor or oncogene, and the use of adjuvant trastuzumab (Herceptin; Roche, Basel, Switzerland) is now the standard of care for these patients. Four large randomised trials[1–3] have clearly shown that trastuzumab has a major effect in reducing recurrence and death in patients with this type of early breast cancer. Initial trials compared 1 year of trastuzumab treatment with a control group without trastuzumab.[1–3] Longer follow-up confirmed a persistent benefit of 1 year of trastuzumab treatment versus observation (no trastuzumab).[4–7] The HERA (HERceptin Adjuvant) trial[1] randomly assigned patients to one of three groups: a control group, 1 year of trastuzumab, or 2 years of trastuzumab. This trial is unique because it assigned patients to 2 years of trastuzumab. Demonstration that 2 years of trastuzumab was not more effective than 1 year of trastuzumab[7] reinforced the use of 1 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. Here we report the results of the

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Research in context

Evidence before this study

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". We found no data in the published literature providing 10 years or more of follow-up from the use of adjuvant trastuzumab within a randomised trial.

Added value of this study

To our knowledge, this 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. We provide long-term patient outcome data to support the use of 1 year of adjuvant trastuzumab in this patient population, with evidence that those patients randomly assigned to receive trastuzumab (in both the 1-year and 2-years groups) sustained relative reductions in recurrence and breast cancer deaths, with the reassurance that the rate of serious toxicity does not increase over time. We also showed no evidence of a benefit of 2 years of trastuzumab compared with 1 year, and could not identify a subgroup of patients studied in the HERA trial who would not have derived long-term benefits.

Implications of all the available evidence

Patients with HER2-positive early breast cancer who meet the criteria for the HERA trial (or the other studies reported elsewhere), including the cardiac disease criteria, we believe should be offered 1 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 10 years after diagnosis, with no evidence of significant differential benefit by disease characteristics, such as nodal status or tumour hormone receptor status. Additionally, there is no evidence of late emergent side-effects, including no evidence of more cardiac endpoints emerging up to 10 years after treatment.

comparison between observation, 1 year of trastuzumab, and 2 years of trastuzumab treatment at a median follow-up of 11 years of patients enrolled within the HERA trial.[1]

Methods

See Online for appendix

Study design, participants, and randomisation and masking

HERA is an open-label, phase 3, randomised controlled trial; full details of the trial methods have been previously reported.[1,5] Briefly, between Dec 7, 2001, and June 20, 2005, 5102 patients were recruited and randomly assigned (1:1:1) to three groups of observation (without trastuzumab), or adjuvant treatment of trastuzumab for 1 year or for 2 years.[1] Methods used to generate the random allocation sequence, stratification factors, type of randomisation, approval of the protocol by local ethics committees at each hospital, and the need for each patient to give signed informed consent are described elsewhere.[5]

The comparison of the trastuzumab groups versus observation was based on the intention-to-treat (ITT) principle, after exclusion of three patients (one from each group) because of no record of written informed consent (figure 1). The comparison of 2 years versus 1 year of trastuzumab was based on a 12-month landmark analysis of the 3105 women who were alive and disease-free for at least 12 months (366 days) after randomisation to one of the two trastuzumab groups.[7] To be eligible to participate, participants had to provide written informed consent and have central laboratory (Kassel, Germany) confirmation of locally assessed HER2-positive disease and left ventricular ejection fraction (LVEF) of at least 55% after completion of all chemotherapy with or without radiotherapy (figure 1). Patients with node-negative disease were eligible for enrolment in the HERA trial if the pathological tumour size was larger than 1 cm. Adjuvant endocrine therapy for women with steroid hormone receptor-positive cancers was administered concomitantly with and after trastuzumab in accordance with local protocols (appendix).

Procedures

Patients assigned to receive trastuzumab received a dose once at 8 mg/kg of bodyweight intravenously, then at 6 mg/kg once every 3 weeks for either 1 year or 2 years depending on group assignment. All patients adhered to the same schedule of follow-up visits, during which the symptoms, side-effects (graded according to the National Cancer Institute Common Toxicity Criteria [NCI-CTC] version 2.0), and findings on clinical examination every 3 months and haematological and chemistry tests every 6 months were recorded for the first 2 years after randomisation. Therefter, clinical and laboratory assessments were scheduled to occur ever 6 months for years 3–5, and then once per year up to year 10. Annual chest radiography was required up to year 5 and annual mammography up to year 10. Study visits for individual patients continued for 10 years after randomisation with full recording of any 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 follow-up visit, the calculation of disease-free survival included the additional follow-up time reported after 10 years and deaths reported during the additional follow-up period were noted as disease-free survival events.

Cardiac monitoring in all three groups included clinical assessments and measurements of LVEF by either echocardiography or multiple gated acquisition (MUGA) scanning at baseline, at months 3, 6, 12, 18, 24, 30, and 36, and annually thereafter up to 10 years from randomisation. A primary cardiac endpoint was defined as New York Heart Association (NYHA) class III or IV toxicity, confirmed by a cardiologist, and a clinically significant 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 clinically significant LVEF drop of at least 10 percentage points from baseline and to an absolute LVEF below 50% confirmed by repeat assessment. An algorithm was defined in the protocol (appendix) prescribing delay or cessation of trastuzumab in response to cardiac endpoints.

Outcomes

This analysis was a pre-planned, final efficacy analysis of the HERA trial. The primary endpoint was disease-free survival, as described previously.[1] Events ending disease-free survival were almost identical to those used to define invasive disease-free survival (IDFS) using STEEP criteria.[8] Secondary endpoints included overall survival, sites of first relapse, competing-risk cumulative incidence analysis of breast cancer and non-breast cancer disease-free survival events, and cardiac safety. Additionally, a secondary endpoint was an efficacy analysis 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. However, 20 patients assigned to 1 year of trastuzumab and 25 patients assigned to 2 years of trastuzumab were allocated to the observation safety population because they never received trastuzumab. Two additional patients randomly assigned 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 that they started trastuzumab. The results from these two additional patients were included in the ITT analysis for 2 years of trastuzumab group, but censored in the safety analysis. Adverse events were assessed from the time of randomisation. Adverse events, including cardiac endpoints, recorded after crossover of patients in the observation group to trastuzumab were excluded.

Statistical analysis

This updated comparison of 1 year of trastuzumab versus observation was based on 1702 patients enrolled in the 1 year trastuzumab group and 1697 patients in the observation group, using an ITT analysis from the time of randomisation. 884 (52%) of the 1697 patients in the observation group selectively crossed over to receive trastuzumab after the release of the initial results of this trial[1] and other trials[2] in 2005, of whom 477 (54%) had hormone-receptor-positive disease and 407 (46%) had hormone-receptor-negative disease (data not shown). As previously described,[5] the selective crossover improved outcomes for the observation group in the ITT analysis, resulting in an underestimation of the true trastuzumab treatment effect that would have been seen if no selective crossover had occurred.

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 (HRs) and 95% CIs.[10] The cumulative incidence of cardiac endpoints based on competing risks was calculated.[11] Exploratory Cox modelling was done to examine interactions between treatment assignment, hormone receptor status, and

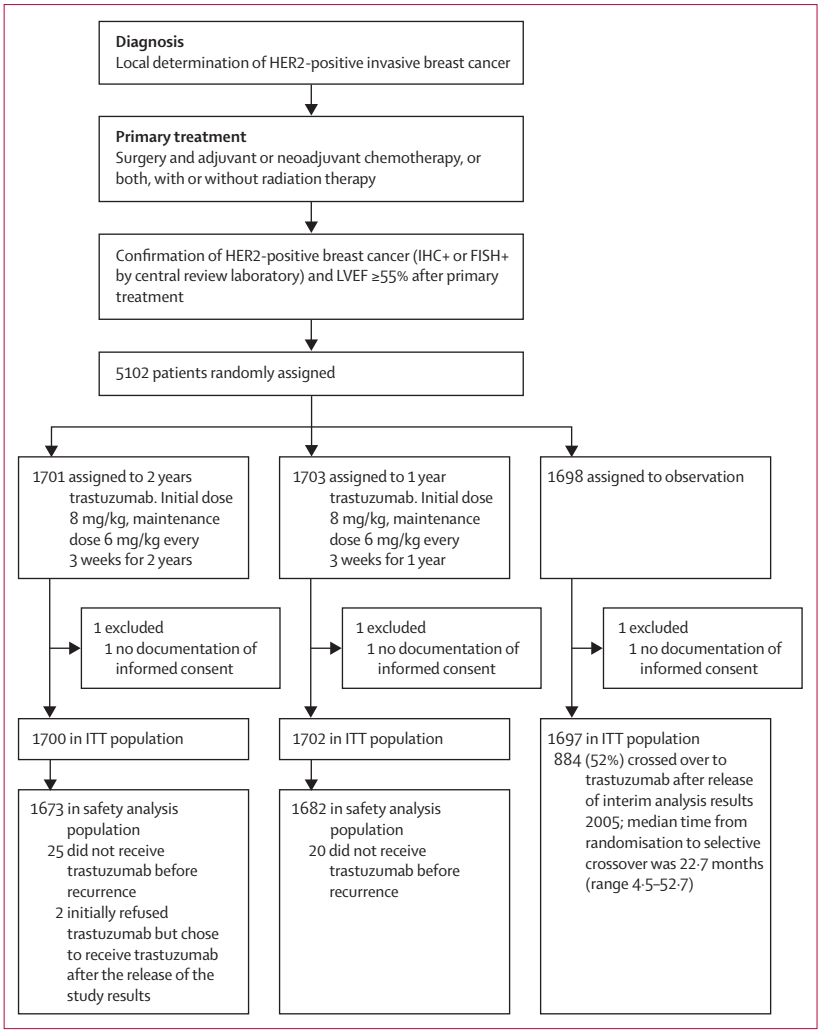

Figure 1: **Trial profile**
IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation. LVEF=left ventricular ejection fraction. ITT=intention to treat.

	Observation (n=1697)	1 year of trastuzumab (n=1702)	2 years of trastuzumab (n=1700)
Age at study entry (years)			
<35	126 (7·4%)	128 (7·5%)	124 (7·3%)
35–49	752 (44%)	756 (44%)	756 (45%)
50–59	546 (32%)	546 (32%)	547 (32%)
≥60	273 (16%)	272 (16%)	273 (16%)
Previous (neo)adjuvant chemotherapy			
No anthracycline	99 (5·8%)	101 (5·9%)	102 (6·0%)
Anthracycline but no taxane	1158 (68%)	1153 (68%)	1158 (68%)
Anthracycline plus taxane	440 (26%)	448 (26%)	440 (26%)
Menopausal status at randomisation			
Premenopausal	234 (14%)	258 (15%)	225 (13%)
Uncertain	691 (41%)	684 (40%)	686 (40%)
Postmenopausal	770 (45%)	760 (45%)	789 (46%)
Pathological tumour size			
Not assessed (neoadjuvant chemotherapy)	178 (10%)	194 (11%)	191 (11%)
0–2 cm	683 (40%)	668 (39%)	652 (38%)
>2–5 cm	724 (43%)	760 (45%)	741 (44%)
>5 cm	96 (5·7%)	71 (4·2%)	106 (6·2%)
Missing size	16 (0·9%)	9 (0·5%)	10 (0·6%)
Nodal status*			
Not assessed (neoadjuvant chemotherapy)	178 (10%)	194 (11%)	191 (11%)
Negative	555 (33%)	543 (32%)	548 (32%)
1–3 positive nodes	490 (29%)	486 (29%)	488 (29%)
≥4 positive nodes	473 (28%)	479 (28%)	473 (28%)
Hormone receptor status (local)†			
Positive (ER or PgR positive, or both)	855 (50%)	859 (51%)	857 (50%)
Negative (ER and PgR negative)‡	842 (50%)	843 (50%)	843 (50%)

Data are n (%). ER=oestrogen receptor. PgR=progesterone receptor. *One patient with missing nodal status in the observation group. †One patient in the 1-year trastuzumab group with unknown oestrogen status and PgR-positive status. ‡Also includes patients with ER negative and PgR unknown.

Table 1: **Baseline demographic and disease characteristics of patients, in the intention-to-treat population**

time on study. Time-varying covariate Cox modelling[11] was used to explore the effect of selective crossover on the risk of a disease-free survival event in the observation control group.

The comparison of 2 years versus 1 year of trastuzumab was based on a 12-month landmark analysis involving the 3105 women who were alive and disease-free for at least 12 months after randomisation to one of the two trastuzumab group. This study is registered with ClinicalTrials.gov, number NCT00045032.

Role of the funding source

The study was conducted under the auspices of the Breast International Group (BIG) and involved the collaboration of 17 BIG groups, nine other cooperative groups, 91 independent centres, and Roche (the sponsor), all of which were represented in the Steering Committee of the HERA trial. The study was designed by members of the HERA Steering Committee.[1] The database was maintained at the Breast European Adjuvant Study Team (BrEAST) Data Centre (Brussels, Belgium). For the final data analysis, the HERA Executive Committee, on behalf of the HERA Steering Committee, had final responsibility for the decision to submit for publication and for the content of the manuscript. The sponsor provided the drug, some site monitoring, and financial support.

Results

Figure 1 shows the trial profile. Three patients had no record of written informed consent and were excluded from analyses. The three groups were well balanced with respect to demographics and baseline disease characteristics including tumour size and nodal and hormone receptor status (table 1).

Overall 2571 (50%) patients had hormone-receptor-positive disease and 2528 (50%) had hormone-receptor-negative disease by local laboratory determination of hormone receptors. 2370 (92%) of the 2571 hormone-receptor-positive cases received adjuvant endocrine therapy. Most patients received chemotherapy only postoperatively, but 563 (11%) patients had preoperative neoadjuvant chemotherapy. Chemotherapy included an anthracycline for 4797 (94%) patients, and an anthracycline and taxane for 1328 (26%) patients. 1646 (32%) patients had node-negative disease. Overall 2642 (52%) patients were aged 49 years or younger at the time of study entry. Patients in the HERA study started trastuzumab at a median of 8·4 months (IQR 7·1–9·6) after initial diagnosis of breast cancer and a median of 89 days (46–112) after completing all chemotherapy.

In this final report, results for 1 year of trastuzumab (median of 18 cycles of once every 3 weeks [one cycle]) versus observation were based on 1113 disease-free survival events (1103 [99%] satisfied the STEEP criteria for IDFS events) and 725 patients deaths (an overall survival event). 884 (52%) patients in the observation group received trastuzumab before a disease-free survival event due to selective crossover after publication of the initial trial results. Despite this selective crossover, using an ITT analysis, after a median 11 years of follow-up the HR was 0·76 (95% CI 0·68–0·86) for 1-year trastuzumab versus observation. For those receiving 2-years trastuzumab (35 cycles median of once every 3 weeks) versus observation the HR was similar at 0·77 (95% CI 0·69–0·87). There were 1126 disease-free survival events for the 2-years trastuzumab versus observation. 10-year disease-free survival was higher in the trastuzumab groups, with 63% in the observation group, 69% in the 1-year trastuzmab group, and 69% in the 2-years trastuzumab group (figure 2A). These figures corresponded with an absolute benefit of 6·8% in disease-free survival at 10 years for those receiving 1-year trastuzumab and 6·0% for those receiving 2-years trastuzumab compared with the observation group. Of note in interpreting the ITT analysis is the fact that about half of the follow-up time in the observation group was accrued after selective crossover to trastuzumab.

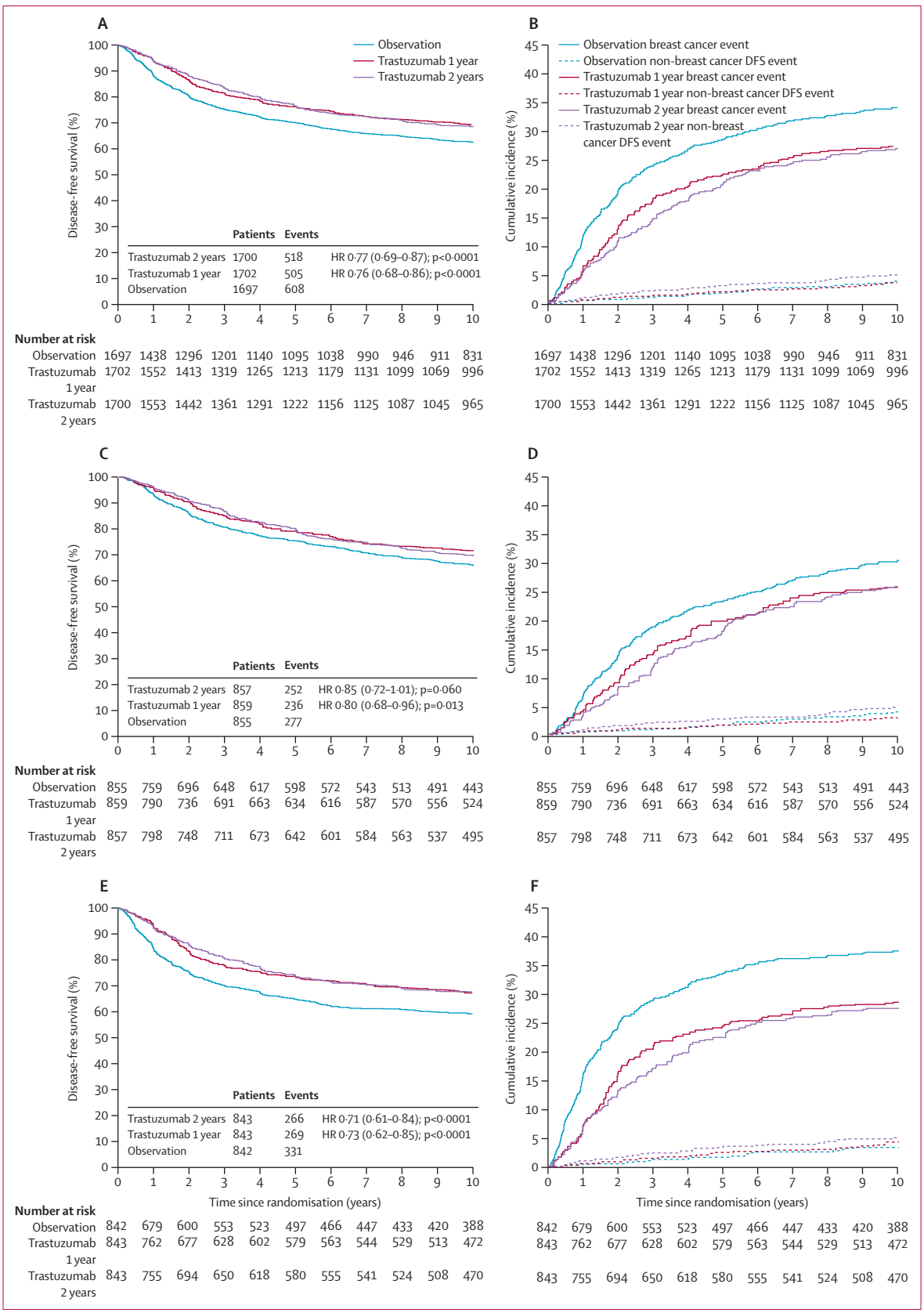

Figure 2: **Kaplan-Meier and cumulative incidence plots for DFS**

Kaplan-Meier plots of disease-free survival (DFS) over time are shown for all the intention-to-treat (ITT) population (A), for patients with hormone-receptor-positive disease (C), and for patients with hormone-receptor-negative disease (E). Cumulative incidence plots for breast cancer and non-breast cancer competing risks are shown for all the ITT population (B), for the hormone-receptor-positive cohort (D), and the hormone-receptor-negative cohort (F). Non-breast cancer DFS events are non-breast malignancy and death without previous event. HR=hazard ratio.

	Intention-to-treat population*			Hormone-receptor-positive cohort*			Hormone-receptor-negative cohort*		
	Observation (n=1697)	1 year of trastuzumab (n=1702)	2 years of trastuzumab (n=1700)	Observation (n=855)	1 year of trastuzumab (n=859)	2 years of trastuzumab (n=857)	Observation (n=842)	1 year of trastuzumab (n=843)	2 years of trastuzumab (n=843)
Patients with an event	608 (36%)	505 (30%)	518 (30%)	277 (32%)	236 (27%)	252 (29%)	331 (39%)	269 (32%)	266 (32%)
Local recurrence	98 (5·8%)	80 (4·7%)	78 (4·6%)	42 (4·9%)	35 (4·1%)	38 (4·4%)	56 (6·7%)	45 (5·3%)	40 (4·7%)
Regional recurrence	29 (1·7%)	18 (1·1%)	24 (1·4%)	13 (1·5%)	7 (0·8%)	16 (1·9%)	16 (1·9%)	11 (1·3%)	8 (0·9%)
Distant recurrence†	383 (23%)	305 (18%)	291 (17%)	177 (21%)	156 (18%)	137 (16%)	206 (24%)	149 (18%)	154 (18%)
CNS	36 (2·1%)	45 (2·6%)	32 (1·9%)	11 (1·3%)	21 (2·4%)	15 (1·8%)	25 (3·0%)	24 (2·8%)	17 (2·0%)
Visceral site	182 (11%)	127 (7·5%)	134 (7·9%)	76 (8·9%)	56 (6·5%)	50 (5·8%)	106 (13%)	71 (8·4%)	84 (10%)
Skeletal	90 (5·3%)	84 (4·9%)	78 (4·6%)	57 (6·7%)	54 (6·3%)	49 (5·7%)	33 (3·9%)	30 (3·6%)	29 (3·4%)
Soft tissue	75 (4·4%)	49 (2·9%)	47 (2·8%)	33 (3·9%)	25 (2·9%)	23 (2·7%)	42 (5·0%)	24 (2·8%)	24 (2·8%)
Contralateral breast cancer‡	38 (2·2%)	42 (2·5%)	45 (2·6%)	14 (1·6%)	14 (1·6%)	21 (2·5%)	24 (2·9%)	28 (3·3%)	24 (2·8%)
Second (primary) malignancy§	40 (2·4%)¶	47 (2·8%)¶	60 (3·5%)¶	21 (2·5%)‖	18 (2·1%)‖	27 (3·2%)‖	19 (2·3%)**	29 (3·4%)**	33 (3·9%)**
Death, no evidence of disease	20 (1·2%)	13 (0·8%)	20 (1·2%)	10 (1·2%)	6 (0·7%)	13 (1·5%)	10 (1·2%)	7 (0·8%)	7 (0·8%)

*In cases with multiple simultaneous sites of first event, a hierarchy assigned the event to the first applicable category in order of 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 of CNS, visceral, skeletal, soft tissue. ‡Includes contralateral invasive disease or ductal carcinoma in situ; there are four disease-free survival events of contralateral DCIS in the intention-to-treat population (two in the hormone-receptor-positive cohort and two in the hormone-receptor-negative cohort), which are not invasive disease-free survival (IDFS) events under the STEEP definition.[8] §Includes second (non-breast) malignancies, invasive ipsilateral tumours of a different type from the primary breast cancer and ipsilateral DCIS events; it does not include contralateral breast cancer of any kind. ¶Eight disease-free survival events of an ipsilateral tumour of a different type from the primary breast cancer reported, which are not IDFS events under the STEEP definition. ‖Three disease-free survival events of an ipsilateral tumour of a different type from the primary breast cancer exist, which are not IDFS events under the STEEP definition. **Five disease-free survival events of an ipsilateral tumour of a different type from the primary breast cancer exist, which are not IDFS events under the STEEP definition.

Table 2: **Site of first disease-free survival event**

The annualised hazard rates for disease-free survival over time are in the appendix. The exploratory time-varying covariate Cox model showed that selective crossover was associated with a reduction in risk of a disease-free survival event in the observation group (HR 0·79, 95% CI 0·64–0·98; appendix). Selective crossover was associated with a numerically lower effect for the hormone-receptor-positive cohort (HR 0·92, 95% CI 0·70–1·22) than for the hormone-receptor-negative cohort (0·69, 0·53–0·91, $p_{interaction}$=0·10; appendix).

In the hormone-receptor-positive cohort, the HR (1-year trastuzumab *vs* observation) was 0·80 (95% CI 0·68–0·96) and the absolute benefit in 10-year disease-free survival rate was 5·6%. The 10-year disease-free survival was 66% in the observation group, compared with 72% in the 1-year trastuzumab and 70% in the 2-years trastuzumab groups (figure 2C). In the hormone-receptor-negative cohort, the 10-year disease-free survival rates were lower; 59% for the observation group, 67% for 1-year trastuzumab group, and 67% for 2-years trastuzumab group. The HR for 1-year trastuzumab versus observation was 0·73 (95% CI 0·62–0·85) and the absolute benefit in 10-year disease-free survival was 8·0% (figure 2E). Exploratory Cox models compared trastuzumab (both 1 year and 2 years combined) versus observation and indicated that time since randomisation was significantly associated with treatment effect for both hormone-receptor-positive and hormone-receptor-negative populations (appendix). HRs for early disease-free survival events (<24 months after randomisation) were 0·63 (95% CI 0·52–0·77) for hormone-receptor-positive and 0·59 (0·50–0·70) for hormone-receptor-negative cohorts (appendix). Corresponding HRs for later disease-free survival events (≥24 months after randomisation) were 0·98 (95% CI 0·82–1·16) for hormone-receptor-positive and 0·91 (0·76–1·09) for hormone-receptor-negative cohorts (appendix).

Subgroup analyses of disease-free survival by nodal status are in the appendix. Disease-free survival was worse for patients with higher numbers of positive axillary lymph nodes. In the 1-year trastuzumab group, the 10-year disease-free survival was 80% for the node-negative cohort, 75% for the cohort with one to three positive nodes, and 55% for the cohort with four or more positive nodes. HRs (1-year trastuzumab *vs* observation) were 0·78 for the node-negative cohort, 0·64 for those with one to three positive nodes, and 0·82 in those with four or more positive nodes.

Table 2 shows the site of first disease-free survival event. The cumulative incidence curves of the competing risk of a disease-free survival event related to breast cancer and of a disease-free survival event not related to breast cancer are shown in figure 2 (B, D, and F). A lower numerical cumulative incidence of disease-free survival events related to breast cancer occurred in each of the trastuzumab groups than in the observation group for both the hormone-receptor-positive and hormone-receptor-negative cohorts. The cumulative incidence of breast cancer-related disease-free survival events was numerically lower in the hormone-receptor-positive cohort, and with a smaller absolute decrease in the trastuzumab groups, than in the hormone-receptor-negative cohort. No numerical decrease

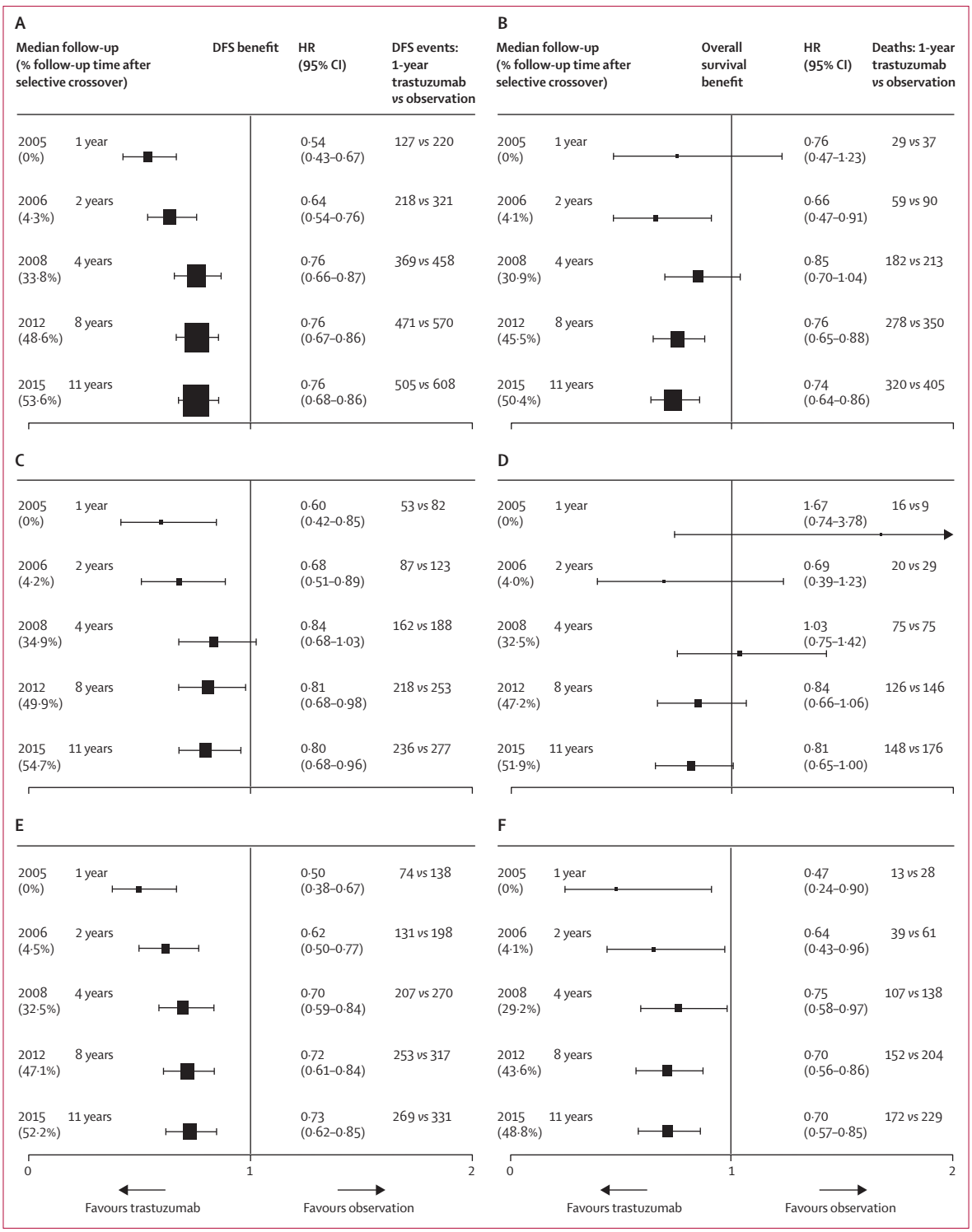

Figure 3: **1 year trastuzumab versus observation, in the ITT population**

Disease-free survival (DFS) for the entire intention-to-treat (ITT) population (A), for patients with hormone-receptor-positive disease (C), and those with hormone-receptor-negative disease (E). Overall survival for the entire ITT population (B), for the hormone-receptor-positive cohort (D), and for the hormone-receptor-negative cohort (F). These ITT analyses are affected by selective crossover in 884 (52%) patients from the observation group who received trastuzumab after the first trial results[1] were published in 2005. HR=hazard ratio. *The percentages are of follow-up time in the ITT analysis that was accrued after selective crossover for patients assigned to the observation group. Figure reproduced and modified from Goldhirsch and colleagues, by permission of Elsevier.[7]

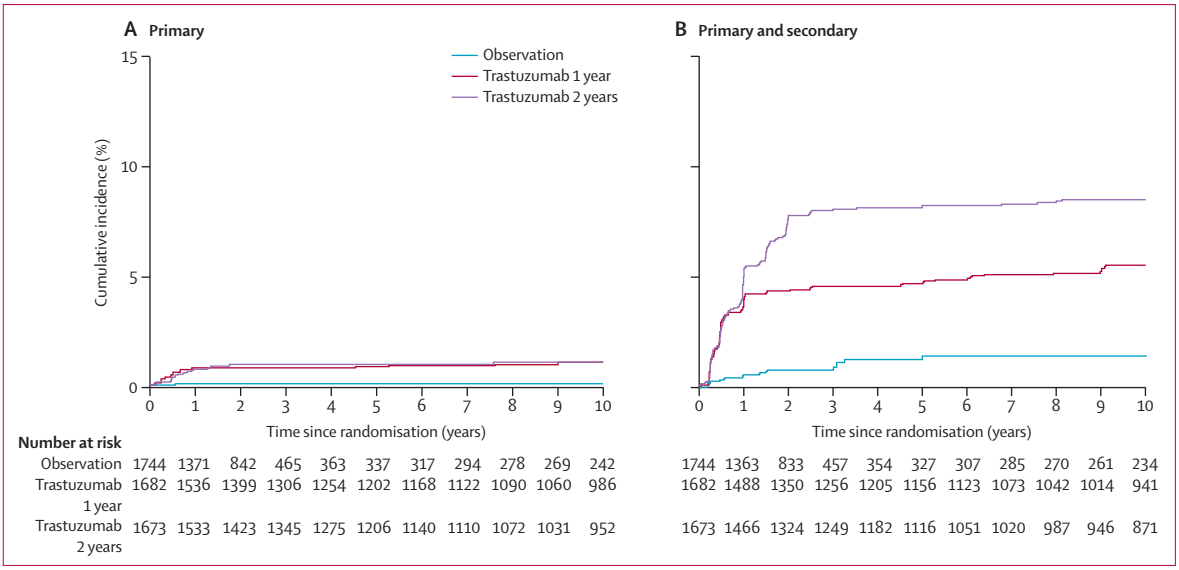

Figure 4: **Cumulative incidence of cardiac endpoints**
Competing risk analysis showing the cumulative incidence of cardiac endpoints with disease-free survival events considered as competing risks. Primary (severely symptomatic) cardiac endpoint (A) and primary and secondary cardiac endpoints (B).

in the incidence of non-breast cancer-related disease-free survival events was noted in either the hormone-receptor-positive or hormone-receptor-negative cohorts. While a clinical benefit of trastuzumab was noted in both the hormone-receptor-positive and hormone-receptor-negative cohorts, the timing and rate of disease-free survival events appears different between these cohorts (figure 2D and 2F).

As with disease-free survival, the results for overall survival also showed a robust and persistent improvement despite the effect of selective crossover (figure 3). The HR (1-year trastuzumab *vs* observation) for overall survival at 11 years of median follow-up was 0·74 (95% CI 0·64–0·86). At 12 years, the overall survival was 73% in the observation group, 79% in the 1-year trastuzumab group, and 80% in the 2-years trastuzumab group. The absolute benefit in 12-year overall survival was 6·5% for 1-year trastuzumab and 6·6% for 2-years trastuzumab (appendix).

In consideration of the overall survival in the hormone-receptor-positive cohort, the HR (1-year trastuzumab *vs* observation) was 0·81 (95% CI 0·65–1·00). At 12 years, the overall survival was 76% in the observation group, 81% in the 1-year trastuzumab group, and 81% in the 2-years trastuzumab group (appendix). In the hormone-receptor-negative cohort, overall survival at 12 years was lower than in the hormone-receptor-positive cohort, with 70% for the observation group, 78% for the 1-year trastuzumab group, and 79% for the 2-years trastuzumab group. The HR for 1-year trastuzumab versus observation was 0·70 (95% CI 0·57–0·85; appendix).

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 (295 [18%] in 1-year trastuzumab; 364 [22%] in 2-years trastuzumab) than in the observation group (152 [9%]; 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 of at least 55% before enrolment. No significant difference was noted in the occurrence of primary cardiac endpoints between the two trastuzumab groups, although the frequency of events was higher than in the observation group (two [0·1%] in the observation group, 18 [1%] in the 1-year trastuzumab group, and 17 [1%] in the 2-years trastuzumab group; figure 4; appendix). Secondary cardiac endpoints occurred more frequently in the 2-years trastuzumab group (122 [7·3%]) than in the 1-year trastuzumab group (74 [4·4%]) and the observation group (15 [0·9%]; figure 4; appendix). In both trastuzumab groups fewer cardiac endpoints occurred after the completion of trastuzumab treatment than in the scheduled treatment period (figure 4). There was no evidence of a clinically significant number of cardiac endpoints occurring after a long time since randomisation (up to 10 years; figure 4).

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 disease-free survival events. There was no evidence of a long-term benefit of 2 years compared with 1 year of trastuzumab when administered as sequential treatment after chemotherapy (HR for disease-free survival 1·02, 95% CI 0·89–1·17; appendix). The short-term separation in the disease-free survival curves in the hormone-receptor-negative cohort was not significant (appendix), for which the long-term HR was 0·94 (95% CI 0·77–1·14; appendix).

In the hormone-receptor-positive cohort the long-term HR was 1·10 (0·91–1·34; appendix).

Discussion

After 11 years of median follow-up, 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 disease-free survival event is reduced by 24% from when trastuzumab is given in addition to standard of care, conferring an absolute benefit of 6·8% improvement in 10-year disease-free survival in those women who were randomly assigned to 1-year trastuzumab group compared with those assigned to the observation group. Furthermore, a 6·5% absolute gain was found in overall survival at 12 years between those in the 1-year trastuzumab group versus those in the observation group. As previously noted,[5] since just over half the patients in the observation group crossed over to receive trastuzumab after release of the initial results of the HERA trial, these estimates of absolute benefit are probably underestimates of the true benefit for patients. In fact, in this analysis selective crossover was associated with a 21% relative reduction in the risk of a disease-free survival event in the observation group, thus clearly attenuating the trastuzumab effect estimated by the ITT analysis. Furthermore, trastuzumab treatment effects were significantly greater during the first 24 months after randomisation than during follow-up, a finding which might be partly attributable to crossover.

Subgroup analysis by tumour hormone receptor status shows two important observations. First, despite overexpression of the *HER2* oncogene, hormone receptor status remains a powerful determinant of disease outcome, with more recurrences and deaths in women with hormone-receptor-negative disease even after 11 years' median follow-up. Furthermore, our data suggest that the timing of recurrences is different, with an initial higher frequency of disease-free survival events in patients with hormone-receptor-negative disease than those with hormone-receptor-positive disease, although events still accumulate up to 10 years after randomisation in both cohorts. Table 2 reports the sites of first recurrence, which clearly shows that all sites of recurrence were slightly more frequent in patients with hormone-receptor-negative HER2-positive breast cancer, with the exception of skeletal distant recurrence, in keeping with previous reports in non-HER2-positive disease. Second, there is no evidence that the efficacy of trastuzumab is different according to the hormone-receptor status of the primary tumour. Numerically the HR was larger in those women with hormone-receptor-positive disease (0·80) than those with homone-receptor-negative disease (0·73; comparing 1-year trastuzumab *vs* observation), but the difference was not significant and could have been affected by the higher percentage of hormone-receptor-positive cases who could cross over due to lower risk of early relapses. Benefit of trastuzumab was also noted in overall survival in both hormone-receptor groups, with lower HRs for 1-year trastuzumab versus observation in the hormone-receptor-negative cohort (0·70) than for the hormone-receptor-positive cohort (0·81).

In earlier reports,[5] there was evidence of progressively smaller apparent benefits of 1 year of trastuzumab in ITT analyses previously reported at 2-year and 4-year median follow-up. The HR for disease-free survival for 1-year trastuzumab versus observation, however, has been stable since 4-year median follow-up (HR 0·76; figure 3). The results show a robust and persistent improvement in disease-free survival despite the effect of selective crossover (figure 3). Despite the increased tendency for patients with hormone-receptor-positive disease to have relapsed later than patients with hormone-receptor-negative disease, the estimated HRs for disease-free survival benefit stabilised at about 4 years of follow-up in both hormone receptor cohorts, suggesting a substantial and permanent effect of 1 year of trastuzumab on micrometastatic disease.

In all analyses of the 1-year trastuzumab group versus observation group for overall survival, fewer deaths were reported in women with hormone-receptor-positive disease than those with hormone-receptor-negative disease. About half of the women enrolled into the HERA trial had hormone-receptor-positive disease, whereas the true proportion in an incident breast cancer population could be nearer to 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 might need a more cautious analysis. If the true benefit in the majority population, which are hormone-receptor-positive tumours, takes longer to appear than hormone-receptor-negative tumours, earlier analyses of overall survival could result in false negative conclusions.

This report includes an updated analysis of a unique feature of the HERA trial, namely addressing the duration question by randomly assigning a third of the patients to a longer, 2-years duration of trastuzumab. The earlier report[7] found no advantage for the longer duration of therapy compared with 1 year of therapy, and is supported by the results from this longer-term analysis. This finding has real clinical relevance because 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 with the combination of two anti-HER2 agents. However, the first report from the ALTTO study of the small molecule HER2 inhibitor lapatinib combined with 1 year of trastuzumab[12] did not find a clinically significant benefit. The only other study that has reported

outcomes for longer than 1 year's anti-HER2 therapy was the ExteNET study.[16] The ExteNET study tested the benefit of 1 year of a small molecule, pan-HER2, tyrosine kinase inhibitor after 1 year of trastuzumab treatment, and the design was altered during the study to report events at 2 years' follow-up in all patients and thus does not have long-term outcome data comparable to those reported here for HERA.

This updated analysis of the HERA study again indicates that a temporary benefit in disease-free survival might exist in those patients with hormone-receptor-negative disease who were randomly assigned to 2 years of trastuzumab compared with the 1 year of trastuzumab group. This result could be due to chance, but with other emerging data it does pose the hypothesis that there might be other ways to enhance the efficacy of this drug 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] substantiate that despite this extended anti-tumour therapy, trastuzumab gives clear additional benefit if given for 1 year, but once this drug 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, no anti-tumour therapy is given. Part of the efficacy of trastuzumab might be due to its ability to induce an immunologically mediated anti-tumour effect,[17] which raises the possibility that concurrent modulation of the immune system, rather than further treatment with an anti-HER2 drug, could be of benefit. One might further conjecture that the transient short-term benefit noted from additional trastuzumab after 1 year is because the extended high 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 might mask the signal of any additional temporary benefit from immune enhancement. Finally, it could be hypothesised that the addition of drugs 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 potential recruiter of that immune response.

A further important finding from this 11-year follow-up analysis is the safety of adjuvant trastuzumab. The unique feature of HERA is that serial LVEF assessment up to 10 years was completed in all patients, which provides more complete cardiac information than other reported adjuvant trastuzumab trials. No new safety signals have emerged despite the extended follow-up, and, particularly, no signal of late cardiac problems emerged, despite the ageing by a decade of the cohort in follow-up that subjected patients to an increased risk of age-related cardiac morbidity. For women who were randomly assigned to receive 2-years trastuzumab, more low-level cardiac endpoints were reported during treatment than for those receiving 1 year of this drug. However, it is reassuring that the frequency of cardiac endpoints during the second year of trastuzumab treatment was similar to that observed during the first year, with few cardiac endpoints reported after 2 years, and evidence showing that those that did occur were mostly reversible.[18] In view of the study eligibility criteria, it is not very surprising that primary cardiac endpoints were rare because the study population was at a low risk for these events.

The selective crossover of just over half of the control group patients is a clear limitation of this extended follow-up ITT analysis of the HERA trial, although it is likely to provide an underestimate of the long-term efficacy of adjuvant trastuzumab. The absence of access to all primary tumour samples precludes exploratory translational analyses that could allow for an increased 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,[1] is essential to inform doctors and patients about the full range of benefits and burdens associated with new widely-adopted treatments. This analysis at a median follow-up of 11 years showed a 24% relative reduction in risk of a disease-free survival event, and a 26% relative reduction in risk of death, with the addition of 1 year of adjuvant trastuzumab in women with HER2-positive early breast cancer. There is no evidence of an additional benefit from a second year of trastuzumab, but some evidence exists of additional cardiac toxicity with longer duration of treatment. These results have been stable during the past several years of additional follow-up. The benefits of 1 year of adjuvant trastuzumab are substantial for both individual patients and breast cancer populations, and might even be underestimated due to the crossover of half of the observation group to receive trastuzumab. The benefits of trastuzumab treatment are noted 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 shows that 1 year of trastuzumab is an important, and curative, part of the standard of care for women with HER2-positive early breast cancer.

Contributors

DC contributed to trial management, literature search, data analysis, data interpretation, manuscript writing, and approval of the final manuscript. MJP-G was principal investigator and involved in trial management, literature search, data analysis, data interpretation, manuscript writing, and approval of the final manuscript. RDG contributed to the study design, data analysis, data interpretation, and manuscript writing. MP contributed to data analysis and interpretation, manuscript writing, and approval of the final analysis.

AG contributed to trial design, data analysis, data interpretation, manuscript writing, and approval of the final manuscript. EdA contributed to trial management, data assembly, data interpretation, manuscript review, and approval of the final manuscript. GC contributed to data interpretation, manuscript writing, and approval of the final manuscript. MU contributed to study design, data collection, data analysis, data interpretation, and manuscript writing. IS contributed to trial management, literature search, data analysis, data interpretation, manuscript writing, and approval of the final manuscript. LG contributed to trial management, literature search, data analysis, data interpretation, manuscript writing, and approval of the final manuscript. JB contributed to the study design, study conduct and coordination, data interpretation, manuscript writing, and approval of the final manuscript. NA-S contributed to trial management, manuscript review, and approval of the final manuscript. SL contributed to trial management, literature search, data analysis, data interpretation, writing of the manuscript and final approval. EM contributed to study design, data collection, trial management, manuscript review, and steering committee and executive committee membership. BL-J contributed to trial design, data analysis, data interpretation, and manuscript review. RB contributed to study design, study conduct (executive committee and steering committee), data interpretation, and writing and review of the manuscript. MD contributed to trial management, data analysis, data interpretation, and approval of the final manuscript. CJ contributed to trial design, trial management, literature search, data analysis, data interpretation, manuscript writing, and approval of the final manuscript.

Declaration of interests

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