2 years versus 1 year of adjuvant trastuzumab for HER2-positive breast cancer (HERA): an open-label, randomised controlled trial

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Summary

Background Trastuzumab has established efficacy against breast cancer with overexpression or amplification of the *HER2* oncogene. The standard of care is 1 year of adjuvant trastuzumab, but the optimum duration of treatment is unknown. We compared 2 years of treatment with trastuzumab with 1 year of treatment, and updated the comparison of 1 year of trastuzumab versus observation at a median follow-up of 8 years, for patients enrolled in the HERceptin Adjuvant (HERA) trial.

Methods The HERA trial is an international, multicentre, randomised, open-label, phase 3 trial comparing treatment with trastuzumab for 1 and 2 years with observation after standard neoadjuvant chemotherapy, adjuvant chemotherapy, or both in 5102 patients with HER2-positive early breast cancer. The primary endpoint was disease-free survival. The comparison of 2 years versus 1 year of trastuzumab treatment involved a landmark analysis of 3105 patients who were disease-free 12 months after randomisation to one of the trastuzumab groups, and was planned after observing at least 725 disease-free survival events. The updated intention-to-treat comparison of 1 year trastuzumab treatment versus observation alone in 3399 patients at a median follow-up of 8 years (range 0–10) is also reported. This study is registered with ClinicalTrials.gov, number NCT00045032.

Findings We recorded 367 events of disease-free survival in 1552 patients in the 1 year group and 367 events in 1553 patients in the 2 year group (hazard ratio [HR] 0·99, 95% CI 0·85–1·14, p=0·86). Grade 3–4 adverse events and decreases in left ventricular ejection fraction during treatment were reported more frequently in the 2 year treatment group than in the 1 year group (342 [20·4%] *vs* 275 [16·3%] grade 3–4 adverse events, and 120 [7·2%] *vs* 69 [4·1%] decreases in left ventricular ejection fraction, respectively). HRs for a comparison of 1 year of trastuzumab treatment versus observation were 0·76 (95% CI 0·67–0·86, p<0·0001) for disease-free survival and 0·76 (0·65–0·88, p=0·0005) for overall survival, despite crossover of 884 (52%) patients from the observation group to trastuzumab therapy.

Interpretation 2 years of adjuvant trastuzumab is not more effective than is 1 year of treatment for patients with HER2-positive early breast cancer. 1 year of treatment provides a significant disease-free and overall survival benefit compared with observation and remains the standard of care.

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Introduction

About 15–20% of breast cancers exhibit overexpression or amplification of the *HER2* oncogene. Trastuzumab substantially reduces disease recurrence and death in patients with this type of early breast cancer and is now used widely in the adjuvant setting. Initial trials compared 1 year of trastuzumab treatment with a no trastuzumab control group.[1–3] Further follow-up confirmed a persistent benefit of 1 year of treatment compared with observation alone.[4–6] The HERceptin Adjuvant (HERA) trial is unique in that it also included randomisation of patients to 2 years of trastuzumab to allow comparison of two different durations of treatment. We report the first results of the comparison of 2 years versus 1 year of adjuvant trastuzumab, and update the comparison of 1 year of trastuzumab versus observation at a median follow-up of 8 years.

Methods

Study design and participants

The HERA trial design, eligibility criteria, randomisation, treatment plan, follow-up and monitoring, and statistical analyses have been described elsewhere.[1,5] Briefly, between Dec 7, 2001, and June 20, 2005, a total of 5102 patients were randomly allocated to three groups: observation, trastuzumab for 1 year, and trastuzumab for 2 years. All patients included had locally assessed HER2-positive early-stage invasive breast cancer confirmed by the central laboratory (in Kassel, Germany), and left ventricular ejection fraction

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See **Comment** page 1010

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(LVEF) of 55% or higher after completion of chemotherapy with or without radiotherapy. The comparison of 2 years versus 1 year of trastuzumab is based on a 12-month landmark analysis of the 3105 women who remained alive and disease-free for at least 12 months (366 days) after randomisation to one of the two trastuzumab treatment groups. Open-label trastuzumab was administered intravenously at an initial dose of 8 mg/kg, followed by a maintenance dose of 6 mg/kg every 3 weeks for 1 year or 2 years. Also presented in this report is an updated comparison of 1 year of trastuzumab versus observation based on 3399 patients enrolled in the two groups, with use of an intention-to-treat analysis from the time of randomisation. All patients gave written, informed consent. The study protocol was approved by ethics review boards at all participating centres.

Randomisation and masking

Random allocation to one of the three groups on a 1:1:1 basis was done within 7 weeks of day 1 of the last chemotherapy cycle or within 6 weeks from the end of radiotherapy or definitive surgery—whichever was last. A minimisation procedure, which followed the methods of Pocock and Simon,[7] was used with stratification by age, worldwide region, nodal status, type of chemotherapy, and hormone-receptor status, together with intention to use endocrine therapy. Randomisation was done at the site under the responsibility of the investigator with an interactive voice response system. The HERA trial is open label.

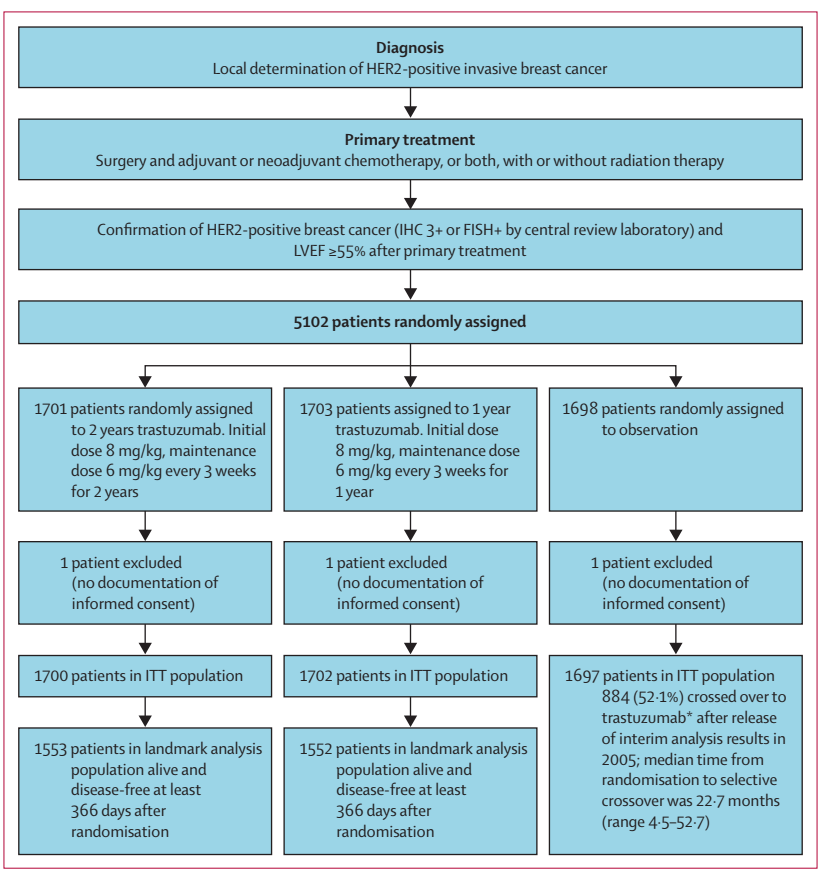

Figure 1: **Trial profile**
IHC=immunohistochemistry. FISH=fluorescence in-situ hybridisation. LVEF=left ventricular ejection fraction. ITT=intention to treat. *During 2012 data cleaning, one of the previously reported 885 selective crossover cases was found to have received trastuzumab after a disease-free survival event (second malignancy).

Follow-up procedures

All patients adhered to the same schedule of follow-up visits, which required recording of symptoms, side-effects (graded according to the National Cancer Institute Common Toxicity Criteria version 2.0), and findings during clinical assessment every 3 months for the first 2 years after randomisation, with haematological and chemistry studies done every 6 months. These assessments were scheduled to occur every 6 months for years 3–5, and then annually up to year 10. Annual chest radiography was needed up to year 5, and annual mammography up to year 10.

Cardiac monitoring and study endpoints

Cardiac monitoring in all groups included clinical assessments and measurements of LVEF by either echocardiography or multigated acquisition scanning at baseline; at months 3, 6, 12, 18, 24, 30, and 36; and annually thereafter up to 10 years after randomisation. A primary cardiac endpoint was defined as New York Heart Association (NYHA) class III or IV, confirmed by a cardiologist, and a 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 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, which prescribed delay or cessation of trastuzumab in response to cardiac endpoints.[8]

The primary endpoint was disease-free survival, as previously defined.[1] For the comparison of 2 years versus 1 year of trastuzumab, disease-free survival was measured from the 12-month landmark. Separate protocol-specified analyses were prospectively planned to be done according to local assessment of the hormone-receptor status of the primary tumour.

Secondary endpoints included overall survival, sites of first relapse, and adverse events (particularly cardiac safety). Safety populations were defined according to randomised assignment, except that 20 patients assigned to 1 year of trastuzumab and 27 patients assigned to 2 years who never actually received the drug were included in the observation group. Adverse events were recorded from the time of randomisation; those that occurred after patients in the observation group crossed over to the trastuzumab group were excluded.

Statistical analysis

The comparison of 2 years versus 1 year of trastuzumab was designed to detect superiority in disease-free survival that was sufficient to yield an HR of 0·80 with 80% power. Two interim analyses were undertaken, and the final analysis was planned when 725 disease-free survival events had been recorded in this comparison. A log-rank test p value of 0·045 or less was required for statistical significance in this final analysis. This report presents results based on 734 events of disease-free survival at a median follow-up of 8 years (7 years after treatments diverged; range 1–10 years).

The efficacy analyses were done according to the intention-to-treat principle. χ^2 tests for categorical data and log-rank tests for time-to-event endpoints provided two-sided p values. Kaplan-Meier curves are presented. The Cox proportional hazards model was used to estimate unadjusted HRs and 95% CIs. SAS software versions 8.2, 9.2, and 9.3 were used for statistical analyses.

Role of the funding source

The study was done 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 the pharmaceutical sponsor, all of which were represented in the Steering Committee of the HERA trial. Members of the Steering Committee designed the study. The database was maintained at the Breast European Adjuvant Study Team data centre in Brussels, Belgium. The datasets extracted from the database for analysis resided in a system of the sponsor, and access was restricted to statisticians of Frontier Science (Scotland) acting on behalf of BIG. The pharmaceutical sponsor had no access to the full database. Interim analyses were presented by the independent statisticians to the Independent Data Monitoring Committee without disclosure to the data centre, the investigators, or the sponsor. The HERA Steering Committee was responsible for the content of the report and for the decision to submit for publication. The sponsor provided the drug, some site monitoring, and financial support.

Results

Figure 1 shows the trial profile. Three patients with no record of written informed consent were excluded from analyses. The cohorts for comparison in the landmark analysis were well balanced in terms of demographics and baseline disease characteristics, including tumour size, node status, and hormone-receptor status (table 1). Overall, local laboratory analysis of hormone receptors showed that about half of the patients had hormone-receptor-positive disease (table 1). 1471 (92·6%) of the 1588 patients with hormone-receptor-positive disease received adjuvant endocrine therapy. 43 (2·8%) of the 1517 patients with hormone-receptor-negative disease received adjuvant endocrine therapy. 2772 (89·3%) patients received chemotherapy only postoperatively: 1386 of 1552 (89·3%) in the 1 year group and 1386 of 1553 (89·2%) in the 2 year group. 333 (10·7%) patients had received preoperative neoadjuvant chemotherapy: 166 (10·7%) of those in the 1 year group and 167 (10·8%) of those in the 2 year group. Previous chemotherapy, either adjuvant or neoadjuvant, included an anthracycline for 2920 (94·0%) of patients and a taxane for 792 (25·5%; table 1). Patients with node-negative disease were eligible for enrolment if the pathological tumour size was larger than 1 cm; 1019 (32·8%) of the patients included in the landmark analysis had node-negative disease. Overall, more than half of patients were 49 years of age or younger at study entry (table 1).

Treatment compliance with randomised assignment of trastuzumab duration was generally good. Of

	1 year of trastuzumab (n=1552)	2 years of trastuzumab (n=1553)
Age at study entry (years)		
<35	113 (7·3%)	110 (7·1%)
35–49	698 (45·0%)	692 (44·6%)
50–59	496 (32·0%)	505 (32·5%)
≥60	245 (15·8%)	246 (15·8%)
Previous (neo)adjuvant chemotherapy		
No anthracycline	94 (6·1%)	91 (5·9%)
Anthracycline but no taxane	1063 (68·5%)	1065 (68·6%)
Anthracycline and taxane	395 (25·5%)	397 (25·6%)
Menopausal status		
Premenopausal	229 (14·8%)	202 (13·0%)
Uncertain	632 (40·7%)	637 (41·0%)
Postmenopausal	691 (44·5%)	714 (46·0%)
Pathological tumour size (cm)		
Not assessed (neoadjuvant chemotherapy)	166 (10·7%)	167 (10·8%)
0–2	626 (40·3%)	607 (39·1%)
>2–5	695 (44·8%)	680 (43·8%)
>5	56 (3·6%)	89 (5·7%)
Missing size	9 (0·6%)	10 (0·6%)
Nodal status		
Not assessed (neoadjuvant chemotherapy)	166 (10·7%)	167 (10·8%)
Negative	510 (32·9%)	509 (32·8%)
1–3 positive nodes	455 (29·3%)	460 (29·6%)
≥4 positive nodes	421 (27·1%)	417 (26·9%)
Hormone-receptor status (local)*		
Positive (ER and/or PgR positive)	790 (50·9%)	798 (51·4%)
Negative (ER and PgR negative)†	762 (49·1%)	755 (48·6%)

Data are number (%). ER=oestrogen receptor. PgR=progesterone receptor. *1471 (92·6%) of the 1588 patients with hormone-receptor-positive disease received adjuvant endocrine treatment: 727 (92·0%) of 790 in the 1 year group and 744 (93·2%) of 798 in the 2 year group; whereas 43 (2·8%) of the 1517 patients with hormone-receptor-negative disease received this treatment (28 of 762 [3·7%] in the 1 year group and 15 of 755 [2·0%] in the 2 year group). †This category also includes 52 patients with ER-negative and PgR-unknown status: 28 (1·8%) in the 1 year group and 24 (1·5%) in the 2 year group.

Table 1: **Demographic and baseline disease characteristics of the patients (12-month landmark analysis)**

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For the **trial protocol** see http://breastinternationalgroup.org/what-we-do/clinical-trials/big-1-01-hera/

patients included in the landmark analysis, 148 (9·5%) of 1552 patients randomly allocated to 1 year of trastuzumab either never started (three patients [0·2%]) or did not complete (145 [9·3%]) the year of treatment. Of 1553 patients randomised to 2 years of trastuzumab, 277 (17·8%) did not complete 2 years of treatment for reasons other than a disease-free survival event: seven (0·5%) never started, 157 (10·1%) discontinued before or at 1 year, and a further 113 (7·3%) discontinued before completing 2 years of treatment.

The clinical cutoff date for this analysis was April 12, 2012, at which time we had recorded 367 disease-free survival events in the 2 year trastuzumab group and 367 in the 1 year group since the 12-month landmark. A comparison of disease-free survival showed no significant difference between groups (HR 0·99, 95% CI 0·85–1·14, p=0·86 from the log-rank test; figure 2A). In predefined exploratory analyses by hormone-receptor status, 2 years of trastuzumab did not improve disease-free survival for either subgroup (figure 2B and 2C). Annualised hazard

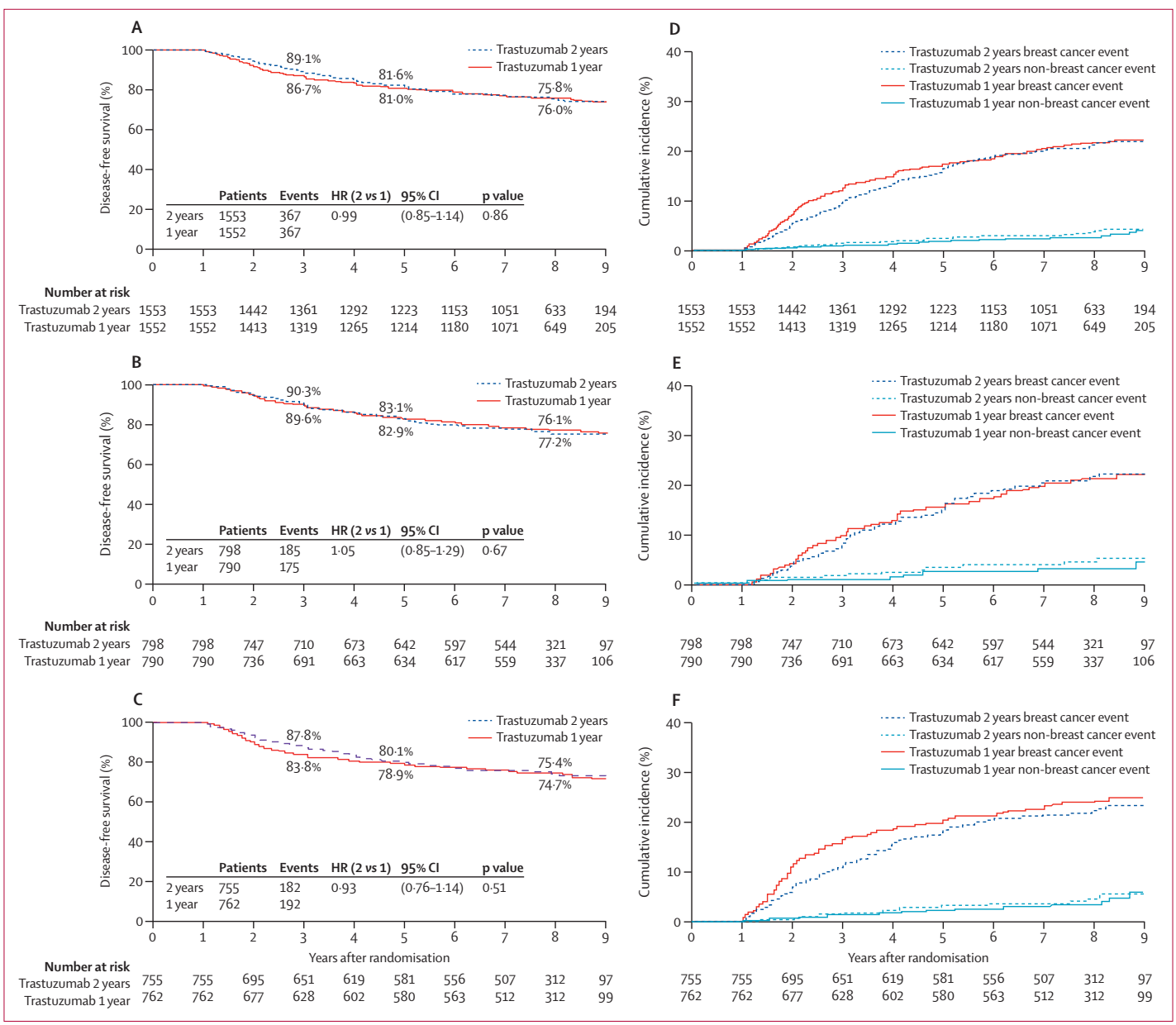

Figure 2: **Kaplan-Meier and cumulative incidence plots for disease-free survival (12-month landmark analysis)**
Kaplan-Meier plots of disease-free survival over time for all 3105 patients in the 12-month landmark analysis (alive and disease-free for at least 366 days after randomisation; A); for patients with hormone-receptor-positive disease (B); and for patients with hormone-receptor-negative disease (C). Cumulative incidence plots for breast cancer and non-breast cancer competing risks are shown for the whole landmark population (D); the hormone-receptor-positive cohort (E); and the hormone-receptor-negative cohort (F).

rate analysis showed that the short-term separation in disease-free survival curves for the hormone-receptor-negative cohort seemed to be due to an excess of events during the first year after treatment cessation in the 1 year trastuzumab group, but the difference was not significant (appendix p 2). The annualised hazard rates for the 2 year trastuzumab group in the hormone-receptor-negative cohort showed a pattern similar to that noted for both treatment groups in the hormone-receptor-positive cohort (appendix pp 3–4). Overall survival did not differ between trastuzumab groups (HR 1·05, 95% CI 0·86–1·28, p=0·63; appendix p 5).

Table 2 shows the types of first event of disease-free survival. Contributions to disease-free survival were assessed separately for breast cancer-related events and competing risks with use of standard cumulative incidence methods[9] (figure 2D–F). Generally, results were similar between the 2 year and 1 year groups, with the exception that breast cancer-related events seemed to be more common in patients with hormone-receptor-negative disease who were assigned to receive only 1 year of trastuzumab (figure 2F), although the difference was not significant. By contrast, we noted no such difference in patients with hormone-receptor-positive disease, almost all of whom were receiving adjuvant endocrine therapy (figure 2E).

More patients had at least one grade 3 or 4 adverse event in the 2 year trastuzumab group than in the 1 year group (table 3). The body systems with the highest frequency of grade 3 or 4 adverse events were: neoplasms benign, malignant, and unspecified (31 [1·8%] in observation group, 60 [3·6%] in 1 year group, and 77 [4·6%] in 2 year group); infections and infestations (12 [0·7%], 37 [2·2%], and 55 [3·3%], respectively); nervous system disorders (12 [0·7%], 14 [0·8%], and 33 [2·0%], respectively); vascular disorders (17 [1·0%], 31 [1·8%], and 33 [2·0%], respectively); cardiac disorders (eight [0·5%], 32 [1·9%], and 32 [1·9%], respectively); musculoskeletal disorders (22 [1·3%], 25 [1·5%], and 28 [1·7%], respectively); general disorders and administration site conditions (eight [0·5%], 17 [1·0%], and 27 [1·6%], respectively); gastrointestinal disorders (six [0·3%], 17 [1·0%], and 28 [1·7%], respectively); injury, poisoning, and procedural complications (12 [0·7%], 18 [1·1%], and 23 [1·4%], respectively). All other body systems had fewer than 20 (<1·2%) patients with grade 3 or 4 adverse events in any group.

Primary (severely symptomatic) cardiac endpoints were rare and their occurrence did not differ between the two treatment groups (figure 3A). Secondary (asymptomatic or mildly symptomatic) cardiac endpoints occurred more frequently in the 2 year treatment group than in the 1 year group (table 3), largely because the constant event rate recorded in both groups during the first year was continued for a second year in the 2 year treatment group (figure 3B). In both groups, cardiac events were rare after completion of trastuzumab treatment.

Separate from the primary landmark analysis, we undertook a descriptive intention-to-treat analysis of the outcome of all three groups from the date of original randomisation (appendix pp 6–9). Importantly, this analysis allows updated comparison of the 1 year treatment group versus the observation-only group, and extends analyses already reported at median follow-up of 1, 2, and 4 years.[1,4,5] The selective crossover of patients randomly allocated to observation after publication of the initial trial results led to 884 (52·1%) of the 1697 patients in the observation group receiving trastuzumab before a disease-free survival event. This occurrence was associated with progressively smaller apparent benefits of 1 year of trastuzumab in previously reported intention-to-treat analyses.[5] The effect of such crossover seems to have abated, in that our results of an intention-to-treat comparison between 1 year trastuzumab and the observation group indicated no further attenuation of benefit and showed a robust and persistent improvement in disease-free survival and overall survival, despite the effect of selective crossover (figure 4). In particular, the HR for disease-free survival at median follow-up of 8 years was

See Online for appendix

	1 year of trastuzumab (n=1552)	2 years of trastuzumab (n=1553)
Number of patients with event	367 (23·6%)	367 (23·6%)
Local recurrence	64 (4·1%)	58 (3·7%)
Regional recurrence	14 (0·9%)	21 (1·4%)
Distant recurrence	223 (14·4%)	208 (13·4%)
Contralateral breast cancer*	29 (1·9%)	31 (2·0%)
Second (primary) malignancy†	32 (2·1%)	39 (2·5%)
Death, no evidence of disease	5 (0·3%)	10 (0·6%)

Data are number of patients (%). In cases with several simultaneous sites of first event, a hierarchy assigned the event to the first applicable category in the following order: distant recurrence, regional recurrence, local recurrence, contralateral breast cancer, and second (primary) malignancy. *Includes invasive disease and/or ductal carcinoma in situ. †Includes second (non-breast) malignancies, invasive ipsilateral tumours of a different type from the primary breast cancer, and ipsilateral ductal carcinoma in-situ events. The category does not include contralateral breast cancer of any type.

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

	Observation only (n=1744)	1 year of trastuzumab (n=1682)	2 years of trastuzumab (n=1673)
At least one grade 3 or 4 adverse event	143 (8·2%)	275 (16·3%)	342 (20·4%)
Fatal adverse event	7 (0·4%)	19 (1·1%)	20 (1·2%)
Primary cardiac endpoint*	2 (0·1%)	14 (0·8%)	16 (1·0%)
Secondary cardiac endpoint†	15 (0·9%)	69 (4·1%)	120 (7·2%)

Data are number of patients (%). *New York Heart Association (NYHA) class III or IV, 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. †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.

Table 3: **Adverse events (safety populations)**

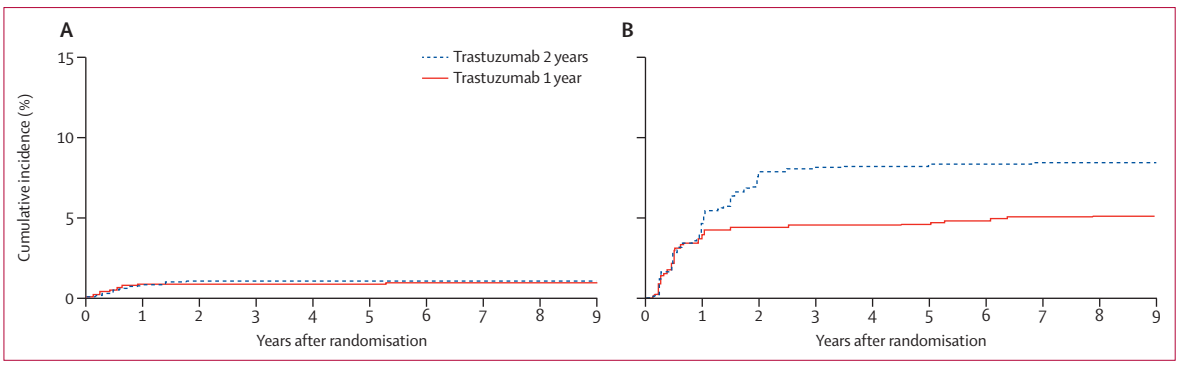

Figure 3: **Cumulative incidence of cardiac endpoints**
Competing risk analysis showing the cumulative incidence of cardiac endpoints with disease-free survival events judged as competing risks. (A) Primary (severely symptomatic) cardiac endpoints. (B) Both primary and secondary cardiac endpoints.

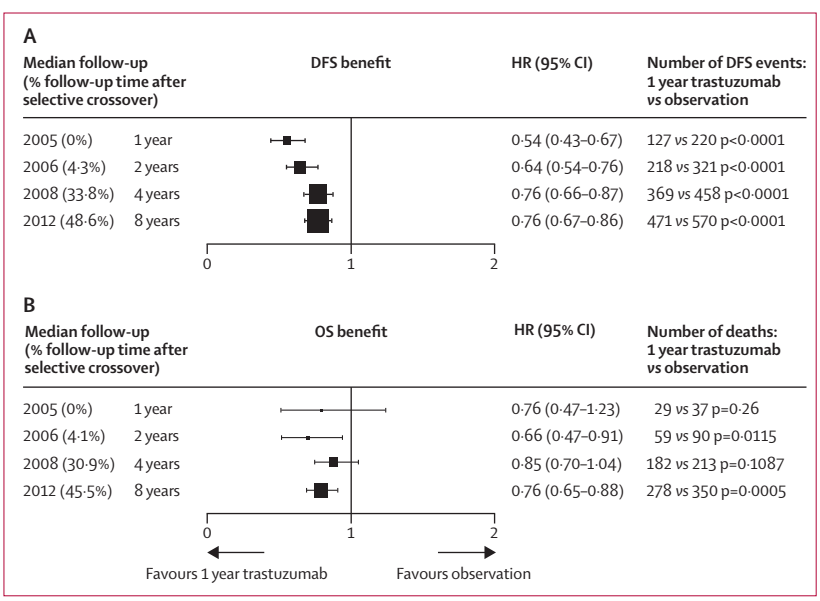

Figure 4: **Hazard ratios and confidence intervals in a comparison of 1 year trastuzumab treatment versus observation (intention-to-treat analysis)**
(A) Disease-free survival. (B) Overall survival. Results for 1, 2, and 4 years' median follow-up are found in references 1, 3, and 4, respectively. These intention-to-treat analyses are affected by selective crossover of 884 (52%) of patients in the observation group who received trastuzumab after the first results were released in 2005. The numbers in parentheses show the percentage of follow-up time in the intention-to-treat analysis that was accrued after selective crossover for patients assigned to the observation group. DFS=disease-free survival. HR=hazard ratio. OS=overall survival.

0·76 (95% CI 0·67–0·86, p<0·0001), and the overall survival HR, which was 0·85 (0·70–1·04) at median follow-up of 4 years, is now 0·76 (0·65–0·88) at 8 years' median follow-up.

Discussion

Patients with HER2-positive early breast cancer given adjuvant trastuzumab have shown substantial improvements in disease-free and overall survival outcomes compared with those given no trastuzumab.[10] Trastuzumab is the most effective targeted drug in breast cancer since tamoxifen. Findings from the HERA trial have supported the beneficial effects of trastuzumab, and this report extends the evidence of a substantial improvement in disease-free and overall survival to a median of 8 years' follow-up. The HERA trial also tested the hypothesis that continuation of trastuzumab treatment beyond 1 year would be superior to 1 year of such treatment. Our results show no such additional benefit, and a small but real increase in adverse events, leading to an unfavourable benefit–risk ratio for 2 years of adjuvant trastuzumab (panel). This finding, together with the high cost of trastuzumab, supports a standard duration of 12 months of adjuvant trastuzumab. This result will be important to many women with early breast cancer and to the health-care systems that treat them. The finding is also important to the validity of the 1 year trastuzumab control groups included in ongoing phase 3 trials in which adjuvant treatments for HER2-positive breast cancer are being investigated.

Predefined subgroup analyses by hormone-receptor status, although not definitive, are intriguing. Within the cohort of patients with hormone-receptor-positive disease, the second year of treatment can be thought of as a comparison between endocrine treatment plus trastuzumab and endocrine therapy alone. By contrast, during the second year of treatment, the hormone-receptor-negative cohort received either trastuzumab alone or no further adjuvant treatment (table 1). The temporary and not statistically significant separation of the curves in favour of 2 years of trastuzumab in the hormone-receptor-negative cohort is indicative of a short-term increased risk of relapse, especially during the second year when these patients receive no adjuvant therapy at all. By contrast, the pattern of relapse in the hormone-receptor-negative cohort receiving a second year of trastuzumab closely resembles that recorded for patients in both groups within the hormone-receptor-positive cohort. The mechanism of such an effect after cessation of all adjuvant therapy at 1 year, if indeed such an effect is biologically real, is unknown. Although these findings are intriguing, they do not provide evidence to support the extension of adjuvant trastuzumab treatment in patients with hormone-receptor-negative disease.

In other trials, investigators have studied the possible benefit of trastuzumab therapy for less than 1 year. The FinHER investigators[11] showed a benefit in terms of disease-free survival from 9 weeks of trastuzumab treatment compared with no trastuzumab, which was similar to the magnitude of benefit noted in the trials of 1 year of trastuzumab, although this conclusion of course involves cross-study comparison. These investigators are doing a randomised trial (the Synergism or Long Duration [SOLD] study) to compare their previous 9 week trastuzumab regimen with 1 year of trastuzumab therapy (NCT00593697). In the SHORT-HER trial (NCT00629278) in Italy, investigators are also assessing 9 weeks versus 12 months of trastuzumab treatment.

A direct randomised comparison of 6 versus 12 months of trastuzumab was undertaken by the PHARE investigators in France, and the first results for 3380 patients at 42·5 months of median follow-up have been reported.[12] The PHARE trial did not show that 6 months of trastuzumab is non-inferior to 12 months (HR 1·28, 95% CI 1·05–1·56, p=0·29 for a non-inferiority HR of 1·15).[12] The PERSEPHONE trial,[13] being undertaken in the UK, and a trial by the Hellenic Oncology Research Group (NCT00615602) are also comparing 6 versus 12 months of adjuvant trastuzumab. Updated results from the PHARE trial and completion of the ongoing trials will be important to ascertain whether patients can be offered a shorter duration of trastuzumab therapy without a compromise on efficacy.

Trastuzumab treatment is associated with an increased risk of cardiac toxicity.[14–16] Patients in the HERA study started trastuzumab at a median of 8·4 months after initial diagnosis of breast cancer and a median of 89 days after completing all chemotherapy, and had to have an LVEF of at least 55% after chemotherapy. In this group, that the incidence of cardiac toxicity was low, particularly in comparison with the recently reported population-based cohort study,[15] is thus not surprising. Almost all cardiac events were recorded during trastuzumab administration, with very few additional events after trastuzumab completion. As reported previously, most of these events were reversible.[14]

The estimate of the advantage in disease-free and overall survival derived from the intention-to-treat analysis comparing 1 year trastuzumab with observation from randomisation is probably conservative since 52% of patients in the observation group chose to receive trastuzumab after the initial trial results, and almost 50% of the follow-up time in the intention-to-treat observation population accrued after this crossover. However, the attenuating effect of this crossover was mostly seen in the early years of follow-up. There has been no potential for additional crossover since the 4 year median follow-up analysis,[5] and the estimate of the overall survival advantage has indeed improved.

On the basis of previous publications showing the worth of the arbitrarily selected duration of 1 year of trastuzumab,[1–3] a de-facto standard of care of 12 months of adjuvant trastuzumab has been established in practice. Our results showed an unfavourable benefit–risk ratio for 2 years of trastuzumab therapy, and thus support the continuation of the 1 year standard duration of treatment.

Panel: Research in context

Systematic review

When the HERceptin Adjuvant (HERA) trial was started in 2001, trastuzumab had been shown to be effective for HER2-positive metastatic breast cancer. HERA was one of several trials done at that time to assess the role of trastuzumab compared with no trastuzumab in the adjuvant setting. The large phase 3 trials (namely HERA, NCCTG N9831, NSABP B-31, and BCIRG 006) assessed trastuzumab administered for the arbitrary duration of 1 year. HERA was unique among these trials because of its inclusion of a third randomised group given trastuzumab for 2 years.

Interpretation

With a median of 8 years' follow-up, the HERA trial has shown that 2 years of trastuzumab treatment has an unfavourable benefit–risk ratio compared with 1 year of treatment. Other trials of durations shorter than 1 year have yet to show equivalence to 1 year of treatment. Thus, 1 year of adjuvant trastuzumab remains the de-facto standard of care for patients with HER2-positive early breast cancer—a treatment approach that is supported by our findings in this report.

Contributors

AG contributed to the study design, data interpretation, and writing of the report. RDG, LG, and CJ contributed to the study design, data analysis, data interpretation, and writing of the report. MJP-G was Principal Investigator and contributed to the study design, patient record, and report revision. EdA and DC contributed to the study management, data analysis, and data interpretation, and writing of the report. MP contributed to the statistical analysis and writing of the report. TMS contributed to the study design, data analysis, and data interpretation. HAW contributed to the preparation of the study protocol, data analysis plan, data interpretation, and report revision. DH contributed to the data analysis, data interpretation, and writing of the report. LDL contributed to the protocol development, data collection, medical review, and writing of the report. EM contributed to the protocol development, study setup, and ongoing management, including Executive and Steering Committee membership, data management, and writing of the report. MD contributed to data interpretation and the biomarker review. MU contributed to the study design, data collection, data analysis, and writing of the report. RB contributed to the study design, study conduct and analysis, data interpretation, and writing of the report. C-HK and AV contributed to data collection and report review. MA contributed to the data collection, data interpretation, and writing of the report. AMB treated and followed up patients, and contributed to writing of the report. DO-R contributed to data collection. SS contributed to data collection and report review. IS contributed to study design, data interpretation, and writing of the report. BL-J contributed to the study design and was on the Steering Committee for the study execution. JB contributed to the study design, study conduct and coordination, data interpretation, and writing of the report.

Conflicts of interest

RDG has received grants as support for his academic salary from Breast International Group, Roche, GlaxoSmithKline, Pfizer, Merck, Celegene, and Novartis, and travel fees from Roche. MJP-G has received honoraria or consulting fees from Roche-Genentech. EdA has received honoraria from Roche. MP's institution has received funding from Roche for the HERA trial. TMS has received a grant from Roche to investigate the basic mechanisms of VEGF inhibitor-induced cardiovascular side-effects, is on the speakers' bureau from Ratiopharm Austria, and has received travel support from Roche. CJ has received academic honoraria from Roche,

GlaxoSmithKline, and Amgen, and travel grants from Roche. DC's institution has received consultancy and lecture fees from Roche and GlaxoSmithKline. HW is employed by the sponsor (Roche) and holds Roche stocks. DH works at F Hoffmann-La Roche and owns non-voting shares in Roche. EM has received grants as support of salary to Frontier Science from Roche and GlaxoSmithKline. MD is on the advisory board for, and is a recipient of grant funding from, Roche. LG has received consultancy or adviser fees from Roche, Genentech, GlaxoSmithKline, Novartis, Pfizer, Boehringer Ingelheim, AstraZeneca, Celgene, BioScience, and Tahio. RB has received consultancy fees from Roche. MA has received honoraria and travel grants from Roche. AMB has received honoraria for advisory boards and lecturing and sponsorship to attend meetings from F Hoffmann-La Roche. IS has received honoraria from Roche. JB has received consultancy fees from Roche-Genentech. All other authors declare that they have no conflicts of interest.

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