

6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer (PHARE): a randomized phase 3 trial

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Summary

Background Since 2005, 12 months of adjuvant trastuzumab has been the standard treatment for patients with HER2-positive early-stage breast cancer. However, the optimum duration of treatment has been debated. We did a non-inferiority trial of a shorter exposure of 6 months versus the standard 12 months of trastuzumab for patients with early breast cancer.

Methods We did an open-label, randomised, phase 3 trial in 156 centres in France. Patients with HER2-positive early breast cancer who had received at least four cycles of chemotherapy, had breast-axillary surgery, and had received up to 6 months of trastuzumab (administered by intravenous infusions over 30–90 min every 3 weeks; initial loading dose 8 mg/kg; 6 mg/kg thereafter) before randomisation were eligible. Patients were randomly assigned via central randomisation procedure with web-based software to continue trastuzumab for another 6 months (12 months total duration; control group) or to discontinue trastuzumab at 6 months (6 months total duration; experimental group). Randomisation was stratified by concomitant or sequential administration of trastuzumab with chemotherapy, oestrogen-receptor status, and centre using a minimisation algorithm. The primary endpoint was disease-free survival, with a prespecified non-inferiority margin of 1.15. Analyses were done in the intention-to-treat population. This study is registered at ClinicalTrials.gov, number [NCT00381901](https://clinicaltrials.gov/ct2/show/study/NCT00381901).

Findings 1691 patients were randomly assigned to receive 12 months of trastuzumab and 1693 to receive 6 months of trastuzumab; 1690 patients in each group were included in the intention-to-treat analyses. After a median follow-up of 42.5 months (IQR 30.1–51.6), 175 disease-free survival events were noted in the 12-month group and 219 in the 6-month group. 2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-month group (hazard ratio 1.28, 95% CI 1.05–1.56; $p=0.29$). 119 (93%) of the 128 cardiac events (clinical or based on assessment of left ventricular ejection fraction) occurred while patients were receiving trastuzumab. Significantly more patients in the 12-month group experienced a cardiac event than did those in the 6-month group (96 [5.7%] of 1690 patients vs 32 [1.9%] of 1690 patients, $p<0.0001$).

Interpretation After 3.5 years follow-up, we failed to show that 6 months of treatment with trastuzumab was non-inferior to 12 months of trastuzumab. Despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care.

Funding French National Cancer Institute.

Introduction

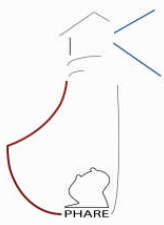
In 2005, results of four clinical trials comparing 12-month duration of trastuzumab given as adjuvant treatment versus observation showed a benefit for patients with HER2-overexpressed early breast cancer.^{1, 2 and 3} On the basis of these results, the US Food and Drug Administration and the European Medicines Agency approved the use of 12 months of trastuzumab in this setting. However, the optimum duration of trastuzumab is debatable. The potential for better efficacy motivated an assessment of 2 years of trastuzumab in the HERA trial.¹ Arguments for shorter exposure were supported

by concerns for cardiac safety^{1, 2 and 3} as well as the results in the subset of patients with HER2-positive tumours in the FinHer trial,⁴ in which trastuzumab was administered for 9 weeks and the magnitude of benefit seemed similar to the results observed in the pivotal clinical trials. In this context, the French National Cancer Institute sponsored a randomised clinical trial comparing two durations of adjuvant trastuzumab: 6 months versus 12 months. We report efficacy and safety results in the overall population. We also investigated efficacy in subgroups of patients according to combinations of stratification factors.

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Methods

Patients

PHARE (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure) is an open-label phase 3 randomised non-inferiority trial. Patients were eligible if they were women over 18 years of age with histologically confirmed invasive early breast cancer with HER2 overexpression. Patients must have received at least four cycles of chemotherapy, had breast-axillary surgery before randomisation, and had provided signed informed consent. Patients had to have received trastuzumab for up to 6 months to be eligible. HER2-positive status was determined by certified local laboratory using immunohistochemistry or fluorescence in-situ hybridisation. An assessment of left ventricular ejection fraction (LVEF) was required after at least 2 months of treatment before patients could continue trastuzumab. All patients suitable for continuing adjuvant trastuzumab treatment with a signed informed consent were eligible.

The trial was sponsored by the French National Cancer Institute, approved by the central ethical committee on May 15, 2006, and was done in compliance with the principles of Good Clinical Practice and the Declaration of Helsinki. An independent data monitoring committee assessed and monitored the trial.

Randomisation and masking

A central randomisation procedure was used to assign eligible patients in a one-to-one ratio to receive either another 6 months of trastuzumab (12 months total duration; control group) or to discontinue trastuzumab (6 months total duration; experimental group). Investigators faxed the forms to the central office of the French National Cancer Institute, and the treatment group was allocated using TenAlea web-based software. A minimisation algorithm was used (with an 80:20 random element), stratifying treatment allocation according to the timing of administration of trastuzumab with chemotherapy (concomitant vs sequential), tumour oestrogen-receptor status (positive vs negative), and centre.

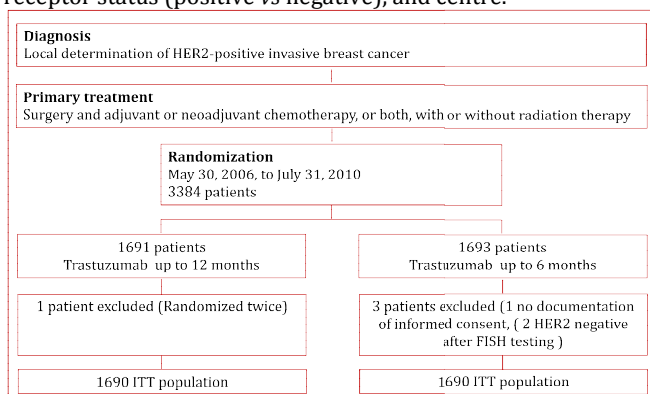


Figure 1: Trial profile

FISH=fluorescence in-situ hybridization, ITT=intention in treat.

Procedures

Trastuzumab was administered by intravenous infusions over 30–90 min every 3 weeks (initial loading dose 8 mg/kg; 6 mg/kg thereafter) in both groups. Chemotherapy, hormone therapy, radiation therapy, and treatment schedules were based on investigator choice.

After the completion of trastuzumab treatment, patients were followed-up by clinical examination and LVEF assessed by echocardiogram or a multigated acquisition scan every 3 months during the first 2 years and then every 6 months

afterwards. Trastuzumab stopping rules based on cardiac monitoring were defined in the protocol according to European Medicines Agency requirements.⁵

Cardiac toxicities were assessed with several indicators including symptomatic clinical cardiac adverse events, a decrease of the LVEF under 50% (this decrease was independent from the baseline value), an absolute drop of LVEF of more than 15% from baseline with a LVEF remaining above 50%, and an absolute decrease of 10% from baseline with a LVEF below 50%.

The primary endpoint was disease-free survival, defined as the time from randomisation to the first occurrence of the following events: local, local-regional, or distant relapses; contralateral breast cancer; second non-breast malignant disease; or death from any cause. Patients alive without any predefined event were censored at the time of the last assessment. Secondary endpoints included cardiac safety, overall survival (defined as the time from randomisation and the date of death), and metastasis-free survival (defined as the time from randomisation to first distant relapse). The main analyses were done in the intention-to-treat population. Safety analyses were done for all randomised patients.

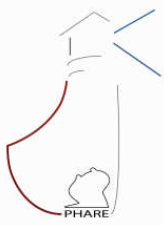
Statistical analysis

Data management was done with the Clinsight 5.5.41.507 software, and statistical analyses were done with Stata version 11.

The null hypothesis of the trial was that 6 months of adjuvant trastuzumab treatment is not inferior to 12-month treatment by a prespecified acceptable margin in terms of disease-free survival. The non-inferiority hazard ratio margin of 1.15 was derived from an estimated absolute difference in 2-year disease-free survival of 2%, based on an expected disease-free survival in the 12-month group of 85% (initially reported by HERA trial¹) and exponential survival. To conclude non-inferiority (ie, reject the null hypothesis), the upper bound of the 95% CI resulting from the comparison between the two arms should be less than this prespecified margin. With a type I error of 5% and 80% power, a total of 1040 events were required for an initial sample size estimate of 7000 patients. The second publication of HERA,⁶ which showed a higher recurrence rate of relapses and had a longer follow-up than in the first report,¹ motivated a change in the sample size for PHARE. The protocol was amended in June, 2007, when only 11% of patients had already been included. The original design called for a 2-year accrual period and an analysis at 4 years. This ambitious design was changed to a 4-year accrual period and an analysis at 8 years, with a reduced sample size of 3400. Because we could expect more events in the same population with a longer follow-up, a smaller number of patients were needed.

In May, 2010, the independent data monitoring committee recommended interruption of recruitment without cross-over and to analyse the data when a 2-year minimum follow-up was attained for all patients. The database was thus locked in July, 2012, which corresponds to 4 years of enrolment and 2 years of follow-up.

All survival rates for each endpoint were estimated using the Kaplan-Meier method. Hazard ratios were estimated using the semi-parametric Cox proportional hazards model. To evaluate the effect of trastuzumab duration, a Cox proportional hazards model was undertaken on the primary endpoint adjusting for the two variables used for stratification. An interaction test at the 0.10 significance level based on the likelihood ratio statistic for the two-way interaction model was used to test for



heterogeneity. Proportionality was tested using Schoenfeld residuals.

Proportions of cardiac toxicities were compared with the log-rank test between the two groups. Additional analyses focusing on cardiac toxicities in PHARE are ongoing.

This study is registered with ClinicalTrials.gov, number [NCT00381901](https://doi.org/10.1185733/NCT00381901).

Role of funding source

The funding source validated the study as designed by the trial's steering committee as well as subsequent amendments. The sponsor organised data collection. Data analysis was done by an independent academic statistician paid for by the sponsor. Data were interpreted by the trial's steering committee, independently from the sponsor. XP, IP, and AK had access to the raw data. The corresponding author had full access to all of the data and had the final responsibility to submit for publication.

Results

From May 30, 2006, to July 9, 2010, 3384 patients were randomly assigned to either 6-month or 12-month treatment with trastuzumab (figure 1). At the time of the present analysis, median follow-up was 42.5 months (IQR 30.1–51.6) from randomisation. During an onsite audit, one patient was found to have been randomised twice within a 2-month interval to the same group, thus the second randomisation was ignored. Another randomised patient did not sign their informed consent form and was excluded. Two other patients were excluded when their HER2 status was found to be negative. 1690 patients in each group were analysed.

Patient characteristics were well-balanced between the two groups (table 1): median age was 55 years, median tumour size was 20 mm, 1505 (44.5%) of 3380 patients had axillary nodal involvement, and 1968 (58.1%) were oestrogen-receptor-positive. 2974 (88.0%) patients received radiotherapy and 1690 (50.0%) received adjuvant hormonal therapy. Chemotherapy regimens were similarly distributed between the two arms; 2478 (73.3%) patients received a regimen containing both an anthracycline and a taxane. Most patients (1893 [55.8%]) received trastuzumab concomitantly with chemotherapy; concomitant administration was more frequently used than was sequential administration during the last 2 years of trial accrual. Median follow-up was 37.9 months (IQR 27.1–48.7) for patients treated by concomitant trastuzumab and chemotherapy and 47.5 months (36.2–54.5) for those treated by sequential trastuzumab and chemotherapy. The mean duration of trastuzumab treatment was 11.8 months (SD 2.03) in the 12-month group and 6.3 months (1.46) in the 6-month group. 118 (7.0%) of 1690 patients in the 12-month group had received trastuzumab for a period shorter than 9 months. Reasons for this shorter treatment period included cardiac toxicities leading to early interruptions (49 [2.9%] patients), other toxicities (14 [0.8%]), patients' personal reasons (29 [1.7%]), early disease progression (three [0.2%]), and other or unknown reasons (24 [1.4%]). In the 6-month group, 93 (5.5%) of 1690 patients had received trastuzumab for a period longer than 9 months because of cardiac events leading to a temporary interruption for patients recovering (three [0.2%]), patients' personal reasons (nine [0.5%]), and other or unknown reasons (81 [4.8%]). No patients had dose reductions in either group.

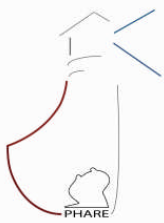
	12-mo group (n=1690)	6-mo group (n=1690)
Age (years)		
<35	62 (3.7%)	66 (3.9%)
35-49	537 (31.8%)	528 (31.2%)
50-59	514 (30.4%)	545 (32.2%)
≥60	577 (34.1%)	551 (32.6%)
Age, median (range)	54 (21 - 86)	55 (23 - 85)
Nodal Status		
Negative	927 (55.4%)	915 (54.7%)
1-3 Pos nodes	502 (30.0%)	506 (30.2%)
≥4 Pos nodes	244 (14.6%)	253 (15.1%)
Missing	17	16
Tumor size (cm)		
<2	905 (54.7%)	866 (52.4%)
≥2 - 5	636 (38.5%)	658 (39.8%)
≥5	113 (6.8%)	129 (7.8%)
Missing	36	37
Scarff-Bloom-Richardson grade		
I	52 (3.1%)	54 (3.3%)
II	679 (41.0%)	672 (40.9%)
III	924 (55.8%)	918 (55.8%)
Missing	35	46
Oestrogen-receptor status		
Negative	716 (42.4%)	696 (41.2%)
Positive	974 (57.6%)	994 (58.8%)
Progesterone-receptor status		
Negative	969 (57.6%)	986 (58.4%)
Positive	712 (42.4%)	701 (41.6%)
Missing	9	3
Hormone receptor		
Negative	669 (39.6%)	650 (38.5%)
Positive	1021 (60.4%)	1040 (61.5%)
Tumor location		
Right	818 (48.4%)	800 (47.3%)
Left	861 (50.9%)	872 (51.6%)
Both	11 (0.7%)	18 (1.1%)
HER2 test results		
IHC HER2+++	1539 (91.1%)	1546 (91.5%)
HER2++ FISH+	111 (6.6%)	106 (6.3%)
HER2++ CISH+	38 (2.2%)	37 (2.2%)
FISH+	2 (0.1%)	1 (0.1%)
Types of chemotherapy		
Taxane and anthracycline-containing regimen	1249 (73.9%)	1229 (72.7%)
Anthracycline-only containing regimen	268 (15.9%)	262 (5.5%)
Taxane-only regimen	171 (10.1%)	196 (11.6%)
Regimen without taxane and anthracycline	2 (0.1%)	3 (0.2%)
Timing of administration chemotherapy and trastuzumab		
Sequential	729 (43.1%)	747 (44.2%)
Concomitant	961 (56.9%)	943 (55.8%)

Data are n(%) unless otherwise stated. IHC=Immunohistochemistry. FISH=Fluorescent in-situ Hybridization. CISH=Chromogenic in situ hybridization. HER2=Human Epidermal Growth Factor Receptor 2.

Table 1. Baseline patient and disease and treatment characteristics

In the overall population, with both treatment groups combined, 2-year disease-free survival was 92.5% (95% CI 91.5–93.3) and 3-year overall survival was 96.0% (95.3–96.7).

394 disease-free survival events were reported: 175 (10.4%) events in the 12-month group and 219 (13.0%) in the 6-month group. 2-year disease-free survival was 93.8% (95% CI 92.6–94.9) in the 12-month group and 91.1% (89.7–92.4) in the 6-



month group. The estimated hazard ratio was 1.28 (95% CI 1.05–1.56) in the univariate Cox model (figure 2). Thus we cannot conclude that the 6-month regimen was non-inferior to the 12-month schedule (p for non-inferiority=0.29). A univariate forest plot including patient, disease, and treatment characteristics related to disease-free survival is shown in figure 3.

The randomisation used a minimisation technique, so a conventional stratified analysis was not strictly applicable. The conventional univariate Cox model gave a hazard ratio of 1.28 (95% CI 1.05–1.58). The hazard ratios whether stratified or adjusted for oestrogen-receptor status and modalities of treatment were the same 1.29 (95% CI 1.06–1.57).

159 (4.7%) patients died, 66 (3.9%) in the 12-month group and 93 (5.5%) in the 6-month group (figure 2). The estimated hazard ratio was 1.46 (95% CI 1.06–2.01), however the test of proportional hazards was significant ($p=0.03$), indicating that proportional hazards cannot reasonably be accepted as plausible for overall survival. Longer follow-up with more events is required to provide mature data for overall survival.

Fewer patients had distant recurrences as first events in the 12-month group than in the 6-month group (108 [6.4%] vs 141 [8.3%]). The estimated hazard ratio was 1.33 (95% CI 1.04–1.71). Other event types were similarly distributed between the two groups (table 2). The metastasis-free survival in the 12-month group was 95.9% (95% CI 94.8–96.7) and in the 6-month group was 93.8% (92.5–94.9). Both stratification factors, oestrogen-receptor status, and mode of administration of trastuzumab with chemotherapy, were significantly related to disease-free survival, and the two-way interaction test in the multivariate model showed significant heterogeneity ($p=0.09$; appendix). Patients with oestrogen-receptor-negative tumours treated with 6 months of sequential trastuzumab chemotherapy had significantly shorter disease-free survival than did patients with oestrogen-receptor-negative tumours treated with 12 months of sequential trastuzumab chemotherapy (hazard ratio 1.57, 95% CI 1.08–2.28; figure 4). However, disease-free survival did not differ between the two randomised groups when analysed based on other combinations of trastuzumab and chemotherapy and oestrogen-receptor status (table 3, figure 4).

Serious adverse events were rare (20 [1.2%] in each group). Early stopping of trastuzumab due to toxicities was reported in 139 (8.2%) patients in the 12-month group and 38 (2.2%) in the 6-month group. Those interruptions were related to cardiac events or decreased LVEF in 103 (6.1%) cases in the 12-month group and 32 (1.9%) cases in the 6-month group. No deaths related to trastuzumab were reported.

Of the 128 cardiac events (clinical or based on LVEF assessment), 119 (93.0%) occurred while patients were still receiving trastuzumab. Significantly more patients who had a cardiac event in the 12-month group than in the 6-month group (96 [5.7%] patients versus 32 [1.9%]; $p<0.0001$). The distribution of cardiac event occurrences varied according to the types of previous exposure of chemotherapy. In the 12-month group, 68 (5.4%) of 1249 patients who received a regimen containing both an anthracycline and a taxane had a cardiac event, compared with 23 (8.6%) of 268 patients who received an anthracycline-containing regimen without taxane, and five (2.9%) of 173 patients who received a regimen without anthracyclines. In the 6-month group, 24 (2.0%) of 1229 patients who received a regimen containing both anthracyclines and taxanes, six (2.3%) of 262 who received a regimen containing anthracyclines but no taxanes, and two (1.0%) of 199 who received a regimen without either

anthracyclines or taxanes had cardiac events. More than 25 000 LFEV assessments were done among the 3380 patients enrolled in PHARE. Significantly more patients had a value of LVEF under 50% in the 12-month group than in the 6-month group: 106 (6.3%) of 1690 patients versus 79 (4.7%) of 1690 patients ($p=0.04$). Again, most events were seen while patients were receiving trastuzumab. No difference was noted between groups in terms of the number of patients who had an LVEF of less than 50% independently of the baseline and a decrease of more than 10% (81 [4.8%] in the 12-month group vs 60 [3.6%] in the 6-month group; $p=0.07$) or in the number of patients who had a decrease of more than 15% from baseline with an LVEF of more than 50% (125 [7.4%] vs 118 [7.0%]; $p=0.64$).

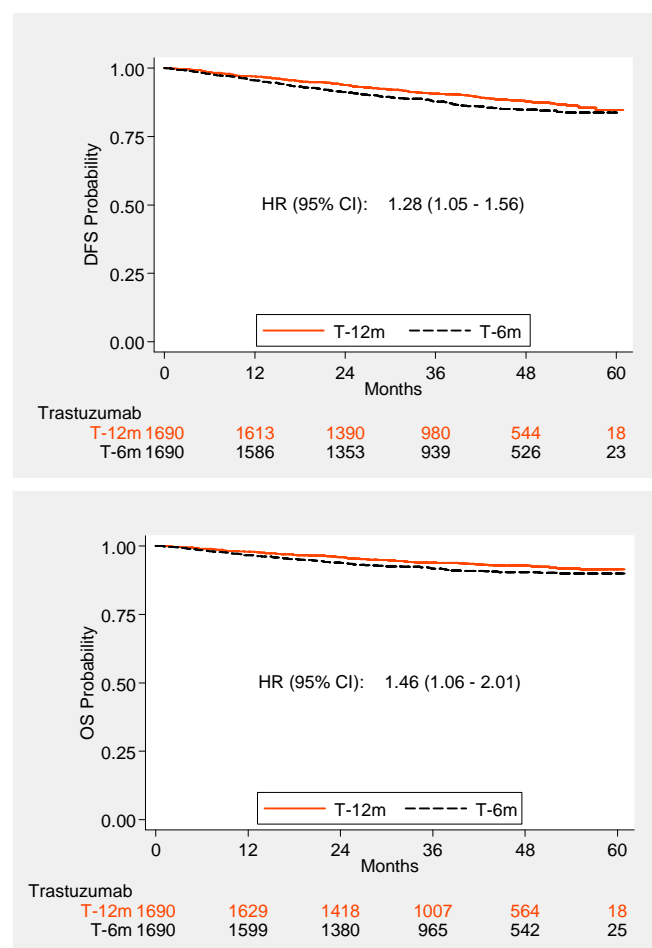


Figure 2: Disease-free survival (A) and overall (B) survival according to trastuzumab duration
 T-12m=12 months of trastuzumab. T-6m=6 months of trastuzumab.
 HR=hazard ratio.

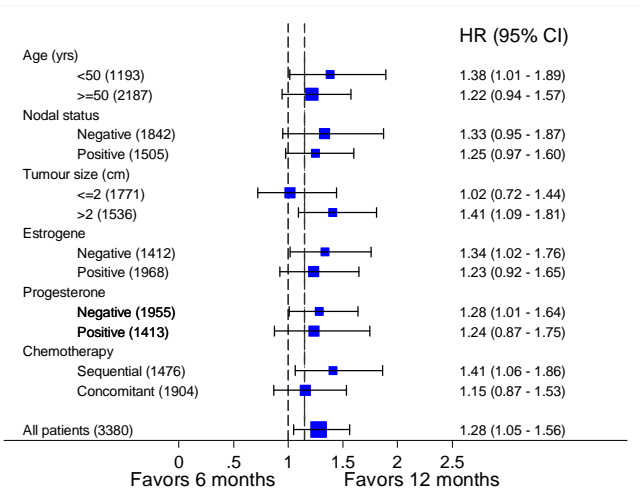
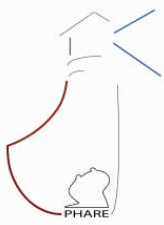


Figure 3: Univariate forest plot for disease-free survival

	12-month group (n=1690)	6-month group (n=1690)
Disease-free survival events	175 (10.4%)	219 (13.0%)
Local Recurrence	19 (1.1%)	23 (1.4%)
Regional Recurrence	10 (0.6%)	9 (0.5%)
Distant Recurrence	108 (6.4%)	141 (8.3%)
Controlateral Breast Cancer	7 (0.4%)	12 (0.7%)
2 nd Primary Malignancy	25 (1.5%)	26 (1.5%)
Death	6 (0.4%)	8 (0.5%)

Table 2: Disease-free survival events

Discussion

This analysis of the PHARE trial, after a median follow-up of 42 months, did not show that 6 months of treatment with adjuvant trastuzumab is non-inferior to 12 months of such treatment for women with HER2-positive early breast cancer. Thus, despite the increased risk of cardiac events with longer treatment duration, 12 months of trastuzumab should remain the standard adjuvant treatment for such patients (panel).

The PHARE trial involved 156 French sites including university hospitals, cancer-care centres, public and private community hospitals, and 350 investigators. The accrual represented around 20% of patients treated with adjuvant trastuzumab in France over the same period. This proportion suggests that the population enrolled in this trial was representative of patients with HER2-overexpressed early breast cancer treated in France. The main characteristics of PHARE patients were similar to the other reported large prospective clinical trials in this population, except for a higher proportion of patients with node-negative disease and small tumour size.

In PHARE, the overall efficacy results for both groups combined were favourable. After a median follow-up of 3.5 years, distant relapses accounted for just under two-thirds of the events in both groups (table 2).

Panel: Research in context

Systematic review

At the time of the study design in 2005, results from three phase 3 trials were available, which showed that 12 months of adjuvant trastuzumab added to chemotherapy provided a benefit versus chemotherapy alone.^{1, 2 and 3} Arguments for shorter exposure were supported by concerns for cardiac safety,^{1, 2 and 3} as well as the subset of patient with HER2-positive tumours in the FinnHer trial⁴ who achieved a similar benefit with only 9 weeks of trastuzumab associated with adjuvant chemotherapy. This study was the first which assessed the adjuvant trastuzumab duration.

Interpretation

PHARE failed to show that 6 months of adjuvant trastuzumab was non-inferior to 12 month adjuvant trastuzumab. The standard treatment should remain as 12 months of adjuvant trastuzumab.

These rates seem lower than the proportion found in other randomised trials. In PHARE, the flexible criteria allowing the inclusion of patients with a medical history of primary cancers or other potentially life-threatening diseases could explain the slightly greater number of events related to second primary cancers (51 [12.9%] of events) and death from any cause (14 [3.6%] of events) than seen in other pivotal trials.^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12} The lower risk profile of our patients compared with those in other trials (less axillary nodal involvement, smaller tumour size), and our trial design, which excluded patients who did not complete adjuvant chemotherapy or who recurred early before the randomisation, selected a population with lower risk of events than the pivotal trials of trastuzumab. This discrepancy could have also affected the distribution of disease-free survival events.

The licensing application for routine use of adjuvant trastuzumab in Europe was based on the results of the HERA trial, which administered trastuzumab and chemotherapy sequentially.⁶ However, concomitant administration of trastuzumab and chemotherapy was not prohibited in the European label. Aware of the potential effect of the different timing of administration of trastuzumab relative to chemotherapy, randomisation was stratified on this factor. Since the presentation of the NCCTG N9831 trials results,¹¹ the proportion of patients in PHARE receiving sequential trastuzumab and chemotherapy decreased, while the proportion receiving the two treatment concomitantly increased.

Non-inferiority trials are still relatively uncommon, but are often used to evaluate de-escalation strategies. Commonly, a per-protocol analysis is recommended for non-inferiority trials,¹³ however, an intention-to-treat analysis was chosen for our analysis. This choice was based on the particular design of PHARE, in which patients were scheduled to be randomised after 6 months of trastuzumab treatment to either continuation for another 6 months or to discontinue. The decision was made to only randomise patients who could potentially continue to receive trastuzumab treatment. A per-protocol analysis was not done due to potential sources of bias. When patients switch the treatment in a non-random way (eg, patients with the poorest prognosis in the 6-month group receive 12 months of treatment) the hypothesis of non-inferiority is favoured.

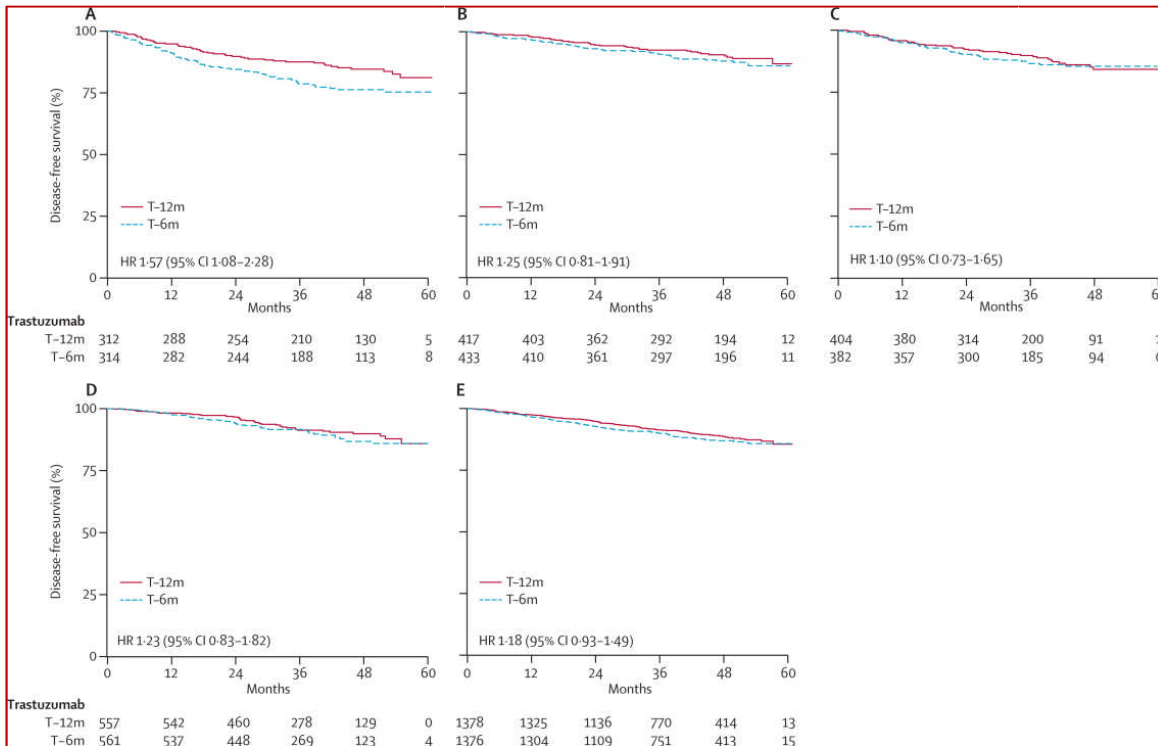
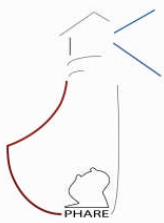


Figure 4: Effect of trastuzumab duration in subgroups defined according to ER-status and timing of trastuzumab administration relative to chemotherapy Oestrogen-receptor negative, sequential chemotherapy and trastuzumab (A). Oestrogen-receptor positive, sequential chemotherapy and trastuzumab (B). Oestrogen-receptor negative, concomitant chemotherapy and trastuzumab (C). Oestrogen-receptor positive, concomitant chemotherapy and trastuzumab (D). Oestrogen-receptor positive or treated with concomitant chemotherapy and trastuzumab (E). T-12m=12 months of trastuzumab. T-6m=6 months of trastuzumab. HR=hazard ratio.

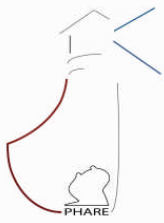
	12-month group		6-month group		Hazard Ratio (95%CI)
	Events/ Patients	Disease-free survival at 2 years (95% CI)	Events/ Patients	Disease-free survival at 2 years (95% CI)	
Total population	1690	93.8% (92.6–94.9)	1690	91.1% (89.7–92.4)	1.28 (1.05–1.56)
Oestrogen-receptor status					
Negative	92/716	91.2% (88.8–93.1)	117/696	87.7% (85.0–89.9)	1.34 (1.02 – 1.76)
Positive*	83/974	95.7% (94.3–96.9)	102/994	93.6% (91.9–95.0)	1.23 (0.92 – 1.65)
Timing of administration of chemotherapy and trastuzumab					
Sequential*	84/729	92.5% (90.3–94.2)	117/747	89.5% (87.0–91.5)	1.41 (1.06 – 1.86)
Concomitant	91/961	94.8% (93.2–96.1)	102/943	92.5% (90.6–94.0)	1.15 (0.87 – 1.53)
Oestrogen-receptor status and timing of chemotherapy and trastuzumab					
Negative – Sequential	46/312	89.8% (85.8–92.7)	69/314	84.5% (80.0–88.1)	1.57 (1.08 – 2.28)
Positive – Sequential	38/417	94.5% (91.8–96.4)	48/433	93.1% (90.2–95.1)	1.25 (0.81 – 1.91)
Negative – Concomitant	46/404	92.3% (89.2–94.6)	48/382	90.3% (86.8–92.9)	1.10 (0.73 – 1.65)
Positive- Concomitant	45/557	96.7% (94.8–97.9)	54/561	94.0% (91.6–95.7)	1.23 (0.83 – 1.82)

*Reference category.

Table 3: Effects of trastuzumab duration according to stratification variables

Further, events leading to treatment interruption (adverse events, relapse, or deaths) and occurring in the 12-month group will most often be imputed to the 6-month group. All these factors created difficulties in defining a clinically sensitive threshold for a per-protocol analysis. The main difficulty in any per-protocol analysis lies in the definition of the population since in all cases the benefit of randomisation is lost.

For these reasons, we considered the intention-to-treat analysis to be preferable for efficacy. We decided to randomise only patients who could potentially continue to receive trastuzumab treatment, which should be taken into account in the interpretation of results. Nevertheless, because the objective was the effect of trastuzumab duration, one could consider that excluding early recurrences and patients with early interruption does not bias the conclusion, since the effect



was similar in the two groups. The results were not affected when we reanalysed the data using the start date of chemotherapy rather than trastuzumab, even if the selection bias of rare early recurrences and interruptions is still present (data not shown).

Only 5% of patients had less than 18 months of follow-up; however, median follow-up is still short, so our results should be interpreted with caution since they could change over time (as seen in the HERA trial).¹² Similarly, due to the small number of deaths, the analysis of overall survival needs longer follow-up.

Randomisation was done while patients were already receiving trastuzumab, which might be one explanation for the low rate of serious adverse events. No deaths related to cardiac events were reported. Nevertheless, the rate of cardiac events and the rates of decrease under 50% of LVEF were significantly higher with longer durations of trastuzumab and suggest the need for further detailed analyses to assess the benefit or risk of longer exposure. Further analyses are underway using these data within a competing risks framework.

We did two-way interaction tests to assess the effect of trastuzumab treatment duration according to the pre-planned stratification factors of oestrogen-receptor status and the timing of administration of trastuzumab relative to that of chemotherapy. Although centre was used as a stratification factor in the minimisation, it was not taken into account in the analysis. This is standard practice in trials with a large number of active centres. However, we compared results for centres grouped according to number of patients included; no significant difference was seen (data not shown). In the model containing only oestrogen-receptor status, timing of administration of trastuzumab relative to chemotherapy, and an interaction term, a significant interaction in terms of disease-free survival was observed. This led us to consider separate analyses for the effect of trastuzumab duration since we could not reasonably ignore the apparent difference in disease-free survival hazard rates within these four subgroups. Further, we believe these subgroup analyses are warranted because of the change over time in the proportion of patients receiving sequential trastuzumab and chemotherapy. Nevertheless, the subgroup analyses should be interpreted with caution. In both treatment groups, the 626 patients with oestrogen-receptor-negative tumours treated with sequential chemotherapy and trastuzumab (accounting for 19% of the total population and 30% of disease-free survival events) had the lowest disease-free survival: 89.8% (95% CI 85.8–92.7) at 2 years in the 12-month group and 84.5% (80.0–88.1) in the 6-month group. The difference between the two groups perhaps contributed, to a large extent, to our failure to show that 6 months of trastuzumab was non-inferior to 12 months. In the 2754 patients with positive oestrogen-receptor status or treated with concomitant chemotherapy and trastuzumab, the effect of a shorter course of trastuzumab was inconclusive. Longer follow-up is needed to reach a conclusion regarding non-inferiority of 6 months of treatment to 12 months of treatment with trastuzumab in any of the subgroups, since the trial was not powered to answer these questions. These results will need to be validated in other ongoing similar trials investigating trastuzumab duration through a pooled analysis. Several trials are currently assessing a shorter duration of trastuzumab, including PERSEPHONE (NCT00712140) and SHORT-HER (NCT00629278). However, on the basis of the results presented here, 12 months of adjuvant trastuzumab should remain the standard of care for women with HER2-positive early breast cancer.

Contributors

PX, IP, AK, and PF designed the study. PX, IP, and AK analysed the data and wrote the report. PX, IP, AK, PF, GR, MD, JYP, PK/TB, AL, and ME interpreted the data. All authors collected the data, revised the report, and agreed to submit the paper for publication.

Conflicts of interest

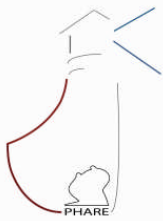
XP receives honoraria from GSK and Roche; GR; MD; JYP receives honoraria and research funding from Roche; PK, receives honoraria from GSK and Roche; ME receives honoraria from Roche; PF receives honoraria from Roche, Aventis, GSK, Johnson & Johnson; DS receives honoraria from Roche, Aventis, GSK and AB science; JPJ receives honoraria from Roche; DK declares conflict of interest Cellgen; IP is an employee of the INCa; AK is on a part time leave of absence from this current employer. The other authors declare no conflict of interest.

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Appendix

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Section 2: Supplementary table 1. Effect of stratification factors (main effects and two-way interaction models) on disease-free survival.

	Main effects model			Nested Interaction model		
	HR	95%CI	p	HR	95%CI	p
ER positive	0.61	(0.50-0.75)	<0.0001	0.52	(0.39-0.68)	<0.0001
Concomitant	0.83	(0.68-1.01)	0.065	0.71	(0.54-0.93)	0.013
Interaction	---			1.41	(0.95-2.09)	0.093
Likelihood Ratio	-3077.38			-3075.96		0.092
Combinations	HR	95%CI		HR	95%CI	
ER - Sequential	1.00			1.00		
ER + Sequential	0.61	(0.50-0.75)		0.52	(0.39-0.68)	
ER - Concomitant	0.83	(0.68-1.01)		0.71	(0.59-0.85)	
ER + Concomitant	0.51	(0.38-0.67)		0.51	(0.39-0.67)	

ER: Estrogen receptor; HR: Hazard Ratio; CI: Confidence Interval