6 months versus 12 months of adjuvant trastuzumab in early breast cancer (PHARE): final analysis of a multicentre, open-label, phase 3 randomised trial

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Summary

Background In 2013, the interim analysis of the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial could not show that 6 months of adjuvant trastuzumab was non-inferior to 12 months. Here, we report the planned final analysis based on the prespecified number of occurring events.

Methods PHARE is an open-label, phase 3, non-inferiority randomised trial of patients with HER2-positive early breast cancer comparing 6 months versus 12 months of trastuzumab treatment concomitant with or following standard neoadjuvant or adjuvant chemotherapy. The study was undertaken in 156 centres in France. Eligible patients were women aged 18 years or older with non-metastatic, operable, histologically confirmed adenocarcinoma of the breast and either positive axillary nodes or negative axillary nodes but a tumour of at least 10 mm. Participants must have received at least four cycles of a chemotherapy for this breast cancer and have started receiving adjuvant trastuzumab-treatment. Eligible patients were randomly assigned to either 6 months or 12 months of trastuzumab therapy duration between the third and sixth months of adjuvant trastuzumab. The randomisation was stratified by concomitant or sequential treatment with chemotherapy, oestrogen receptor status, and centre. The primary objective was non-inferiority in the intention-to-treat population in the 6-month group in terms of disease-free survival with a prespecified hazard margin of 1·15. This trial is registered with ClinicalTrials.gov, number NCT00381901.

Findings 3384 patients were enrolled and randomly assigned to either 12 months (n=1691) or 6 months (n=1693) of adjuvant trastuzumab. One patient in the 12-month group and three patients in the 6-month group were excluded, so 1690 patients in each group were included in the intention-to-treat analysis. At a median follow-up of 7·5 years (IQR 5·3–8·8), 704 events relevant to disease-free survival were observed (345 [20·4%] in the 12-month group and 359 [21·2%] in the 6-month group). The adjusted hazard ratio for disease-free survival in the 12-month group versus the 6-month group was 1·08 (95% CI 0·93–1·25; p=0·39). The non-inferiority margin was included in the 95% CI. No differences in effects pertaining to trastuzumab duration were found in any of the subgroups. After the completion of trastuzumab treatment, rare adverse events occurred over time and the safety analysis remained similar to the previously published report. In particular, we found no change in the cardiac safety comparison, and only three additional cases in which the left ventricular ejection fraction decreased to less than 50% have been reported in the 12-month group.

Interpretation The PHARE study did not show the non-inferiority of 6 months versus 12 months of adjuvant trastuzumab. Hence, adjuvant trastuzumab standard duration should remain 12 months.

Funding The French National Cancer Institute.

Lancet 2019; 393: 2591–98

Published **Online** June 6, 2019 http://dx.doi.org/10.1016/S0140-6736(19)30653-1

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Introduction

Several large randomised clinical trials[1–7] have shown that 1 year of trastuzumab reduces the risk of relapse and death for patients with HER2-positive early breast cancer compared with observation. This 1-year treatment duration has been challenged by several published and ongoing trials. The assessment of a longer 2-year duration of trastuzumab in the HERA trial[8] did not show any significant benefit. A few studies[9–13] have assessed a shorter duration of adjuvant trastuzumab, but the findings have not changed the 1-year standard of care. In 2012, the first analysis[9] of the Protocol for Herceptin as Adjuvant therapy with Reduced Exposure (PHARE) trial did not show that 6 months of adjuvant trastuzumab was non-inferior to 12 months. This first efficacy analysis was requested by the Independent Data Monitoring Committee (IDMC) at a meeting held in May, 2011, because of concerns regarding negative efficacy signals. Of note, the 2012 analysis[9] was based on 394 events and hence was not powered to assess

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See Online for appendix

Research in context

Evidence before this study

In 2005, four trials (HERA, NSABP-B31, NCCTG-N9831, and BCIRG-006) showed the benefit of 12-months of adjuvant trastuzumab for patients with HER2-positive early breast cancer. Since the results of these trials were reported, 12 months of adjuvant trastuzumab has become the standard of care for these patients. However, the optimal duration of adjuvant trastuzumab was unknown. A longer duration was evaluated in the HERA trial, but raised concerns about cardiac safety, supporting a shorter duration. Therefore, in 2005 two randomised studies were designed (Protocol for Herceptin as Adjuvant therapy with Reduced Exposure [PHARE] and PERSEPHONE) to compare 6-month with the standard 12-month trastuzumab treatment duration.

An interim analysis of the PHARE study did not show the non-inferiority of a 6-month treatment duration relative to a 12-month treatment duration; however, this analysis was under-powered to test the non-inferiority of the shorter treatment duration. By contrast, the recent results of the PERSEPHONE study found that the 6-month treatment was non-inferior to the 12-month treatment, since the prespecified non-inferiority margin (1·25) was not contained in the 90% CI (0·93–1·24).

Added value of this study

The final analysis of PHARE was fully powered to test the hypothesis that 6 months of adjuvant trastuzumab is non-inferior to 12 months. Our analysis reinforced the results of the 2012 interim analysis by refuting the non-inferiority of 6 months versus 12 months of adjuvant trastuzumab. The adjusted hazard ratio for disease-free survival in the 12-month cohort versus the 6-month cohort was 1·08 (95% CI 0·93–1·25), which included the prespecified non-inferiority margin (1·15).

Implications of all the available evidence

The PHARE and PERSEPHONE studies assessed the same endpoint with a similar design and reported similar results but reached apparently opposite conclusions. This discordance can be explained by the slightly different prespecified endpoint values in the two studies. The choice of the non-inferiority margin remains inherently controversial, especially in the context of oncology trials in which the primary outcome is survival and any additional death could be considered unacceptable. Hence, the feasibility of non-inferiority trials and reductions in treatment exposure should be questioned. In the specific case of adjuvant trastuzumab, the standard of care should remain as 12 months.

the initial objective of the trial. In this Article we report the final analysis of the PHARE trial, based on the prespecified number of disease-free survival events.

Methods

Study design and participants

The study design, eligibility criteria, patient characteristics, and treatment compliance have been described previously[9] and are summarised herein. PHARE is an open-label, phase 3, non-inferiority randomised trial of patients with HER2-positive early breast cancer comparing 6 months versus 12 months of trastuzumab (F Hoffmann-La Roche, Basel, Switzerland) treatment concomitant with or following standard neoadjuvant or adjuvant chemotherapy. The study was undertaken in 156 centres in France. Eligible patients were women aged 18 years or older with non-metastatic, operable, histologically confirmed adenocarcinoma of the breast and either positive axillary nodes or negative axillary nodes but a tumour of at least 10 mm. Patients must have received at least four cycles of a chemotherapy for this breast cancer; have started receiving adjuvant treatment with trastuzumab; have a baseline left ventricular ejection fraction (LVEF) value measured by echocardiography (Simpson's method) or multigated acquisition scan 3 months (±1 month) after initiation of the treatment with trastuzumab that allows to pursue the treatment; and have overexpression of HER2 in the invasive component of their primary tumour (3+ by immunohistochemistry or 2+ with confirmation of positivity by fluorescence or chemogenic in-situ hybridisation. Exclusion criteria were previous use of anti-HER2 therapy (except trastuzumab); serious cardiac illness or medical conditions not allowing the administration of trastuzumab (ie, history of documented congestive heart failure, high-risk uncontrolled arrhythmias, angina pectoris requiring antianginal medication, severe dyspnoea at rest, or oxygen dependency); known hypersensitivity to trastuzumab or murine proteins; pregnancy or breastfeeding; impossibility of adequate follow-up; or inability to have regular controls because of social, geographical, or psychological reasons.

The trial was approved by the Central Ethics Committee on May 15, 2006, and was done in compliance with the principles of good clinical practice and the Declaration of Helsinki. All participants provided written informed consent.

For the **TenAlea software** see http://fr.tenalea.net

Randomisation and masking

A central randomisation procedure was set up with the TenAlea web-based software. Eligible patients were randomly assigned to either 6 months or 12 months of trastuzumab therapy duration between the third and sixth months of adjuvant trastuzumab. Using a minimisation algorithm, a 1:1 randomisation was stratified according to concomitant versus sequential administration of chemotherapy and trastuzumab, positive versus negative tumour oestrogen-receptor status, and centre.

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 every 3 months during the first 2 years, every 6 months until the fifth year (included), and once a year until the tenth year included. Follow-up visits included clinical exams searching for signs of recurrence, mammography, breast ultrasound, and cardiac left ventricular ejection fraction assessement. Two consecutive missing reports qualified the patients in the group lost to follow-up and they were censored at the date of their last news.

Outcomes

The primary endpoint was disease-free survival, defined as the time from randomisation to the first occurrence of any of the following events: local, regional, or distant relapse; 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 efficacy endpoints included overall survival (the time from randomisation or from start of treatment to death from any cause) and metastasis-free survival (the time from randomisation or from start of treatment to distant relapse or death from any cause, whichever occurred first).

Safety endpoints and compliance were previously reported, as was a dedicated subanalysis of cardiac safety.[9,14] In this analysis we assessed only cardiotoxicity events occurring after completion of trastuzumab treatment. Cardiotoxicity was defined as an absolute decrease in the LVEF to less than 50% regardless of baseline LVEF and an absolute decrease of 10% from baseline with an LVEF of less than 50%.

Statistical analysis

The hypothesis of the PHARE trial was that 6 months of adjuvant trastuzumab is not inferior to 12 months in terms of disease-free survival. The prespecified non-inferiority margin in the protocol was set to 15% in relative terms, corresponding to a hazard ratio (HR) of 1·15. In absolute terms, this difference corresponds to a 2% difference in disease-free survival at 2 years—ie, from 85% (as estimated in the HERA trial[1]) to 83%, assuming an exponential survival distribution.[1]

In 2011, because of a negative efficacy signal associated with the 6-month group, the IDMC recommended stopping patient accrual and continuing patient follow-up until July, 2012—which corresponds to 4 years of enrolment and a minimum of 2 years of follow-up before releasing the data. Hence, an amended statistical plan was written in August, 2011, which prespecified this first analysis requested by the IDMC at an unplanned interim stage and planned the final analysis on the basis of an adequate number of events. With the goal of preserving the non-inferiority margin of 1·15, 680 disease-free survival events were required in the final analysis to claim non-inferiority with 80% power at a 5% two-sided significance level.

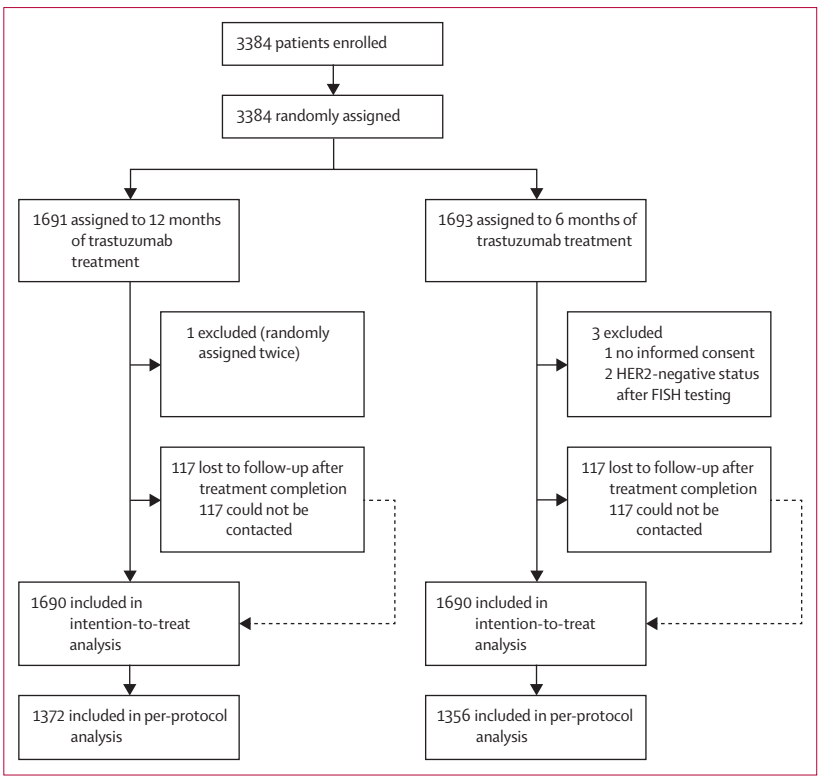

Figure 1: **Study profile**
FISH=fluorescence in situ hybridisation.

This final analysis of the PHARE trial was based on the data cutoff date on Dec 14, 2017. This database is preserved at the French National Cancer Institute.

The main analyses were done in the intention-to-treat population. A sensitivity analysis was done in the per-protocol population defined as the intention-to-treat subgroup of patients who actually received trastuzumab for 6 months within 1 month in the 6-month group, and for 12 months within 2 months in the 12-month group.

All survival estimates for each time-to-event endpoint were estimated using the Kaplan-Meier method and the 95% CI. HRs for the treatment effect (6 months *vs* 12 months), along with their 95% CIs, were estimated using the proportional hazards Cox model adjusted for the stratification factors, which were oestrogen-receptor status (negative *vs* positive) and timing of trastuzumab and chemotherapy (sequential *vs* concomitant); we did not include stratification by centre in the calculation of the adjusted HRs. The same analyses were done in a multivariate Cox model adjusted for treatment group (6 months *vs* 12 months), oestrogen-receptor status (negative *vs* positive), progesterone-receptor

	12-month group (n=1690)	6-month group (n=1690)
Age (years)		
<35	62 (3·7%)	66 (3·9%)
35–49	538 (31·8%)	528 (31·2%)
50–59	514 (30·4%)	545 (32·2%)
≥60	576 (34·1%)	551 (32·6%)
Median (range)	54 (21–86)	55 (23–85)
Nodal status*		
Negative	927 (55·4%)	915 (54·7%)
1–3 positive nodes	502 (30·0%)	506 (30·2%)
>3 positive nodes	244 (14·6%)	253 (15·1%)
Missing data	17	16
Tumour size* (cm)		
<2	742 (44·9%)	703 (42·5%)
≥2–<5	734 (44·4%)	753 (45·6%)
≥5	178 (10·8%)	197 (11·9%)
Missing data	36	37
Scarff-Bloom-Richardson grade*		
I	52 (3·1%)	54 (3·3%)
II	679 (41·0%)	672 (40·9%)
III	925 (55·9%)	918 (55·8%)
Missing data	34	46
Oestrogen receptor status		
Negative	715 (42·3%)	695 (41·1%)
Positive	975 (57·7%)	995 (58·9%)
Progesterone receptor status*		
Negative	969 (57·6%)	986 (58·4%)
Positive	712 (42·4%)	701 (41·6%)
Missing data	9	3
Hormone (oestrogen and progesterone) receptor status		
Negative	670 (39·6%)	650 (38·5%)
Positive	1020 (60·4%)	1040 (61·5%)
Tumour location		
Right	818 (48·4%)	800 (47·3%)
Left	860 (50·9%)	872 (51·6%)
Both	12 (0·7%)	18 (1·1%)
HER2 overexpression or amplification test results		
IHC HER2+++	1539 (91·1%)	1546 (91·5%)
IHC HER2++, FISH+	111 (6·6%)	106 (6·3%)
IHC HER2++, CISH+	38 (2·2%)	37 (2·2%)
FISH+	2 (0·1%)	1 (0·1%)
Types of chemotherapy		
Taxane and anthracycline	1249 (73·9%)	1229 (72·7%)
Anthracycline only	268 (15·9%)	262 (15·5%)
Taxane only	171 (10·1%)	196 (11·6%)
Without taxane or anthracycline	2 (0·1%)	3 (0·2%)
Timing of chemotherapy and trastuzumab administration		
Sequential	718 (42·5%)	729 (43·1%)
Concomitant	972 (57·5%)	961 (56·9%)

Data are n (%) unless otherwise stated. IHC=immunohistochemistry. FISH=fluorescent in-situ hybridisation. CISH=chromogenic in-situ hybridisation. *Percentages are calculated with n=1690–number of patients with missing data.

Table: **Baseline patient, disease, and treatment characteristics**

status (negative *vs* positive), nodal status (negative *vs* positive), tumour size (<2 cm *vs* ≥2 cm), and timing of trastuzumab and chemotherapy (sequential *vs* concomitant).

Proportional hazards were tested using Schoenfeld residuals,[15] and smoothed HRs are presented. When the proportional hazards assumption did not hold, the restricted mean survival time (RMST) was estimated within each group, and the difference and ratio of RMST were estimated, along with the 95% CI, by bootstrap simulation.[16,17] A positive difference or a ratio greater than 1 indicates a result favouring the 12-month group.

The consistency of treatment effect was assessed across prognostic-factor subgroups, and the treatment by subgroup interaction was tested in a Cox model adjusted for each prognostic factor separately. The potential influence of each prognostic factor on the first disease-free survival was also assessed in a Cox model adjusted for each prognostic factor separately.

Analyses were done using SAS (version 9.4).

The analysis and interpretation of the results in this paper were done independently under the auspices of the PHARE executive committee, and an IDMC assessed and monitored the trial. The study was registered with ClinicalTrials.gov, number NCT00381901.

Role of the funding source

The funder of the study was responsible for data collection but had no role in study design, data analysis, or data interpretation. XP, JMG, and the funder of the study had full access to all the data in the study and XP had final responsibility for the decision to submit for publication.

Results

From May 30, 2006, to July 9, 2010, 3384 patients were enrolled and randomly assigned to either 6 months (n=1693) or 12 months (n=1691) of trastuzumab treatment (figure 1). During an on-site audit, one patient was found to have been randomly assigned twice to the 12-month group within a 2-month interval; thus, the second randomisation was excluded. Three patients in the 6-month group were excluded from the study (one did not provide their informed consent and two were found to have a negative HER2 status). Therefore, 1690 patients in each group were included in the analyses. In both groups, 117 (6·9%) of 1690 patients were lost to follow-up over time. At the time of this analysis, the median follow-up for the 3380 patients was 7·5 years (IQR 5·3–8·8) from randomisation. Patient, disease, and treatment characteristics were well balanced between the two treatment groups (table), as previously reported.[9]

704 disease-free survival events were reported, of which 345 (20·4%) were in the 12-month group and 359 (21·2%) in the 6-month group. There were 163 (9·6%) distant recurrences in the 12-month group and 187 (11·1%) in the 6-month group; 53 (3·1%) local-regional relapses in the

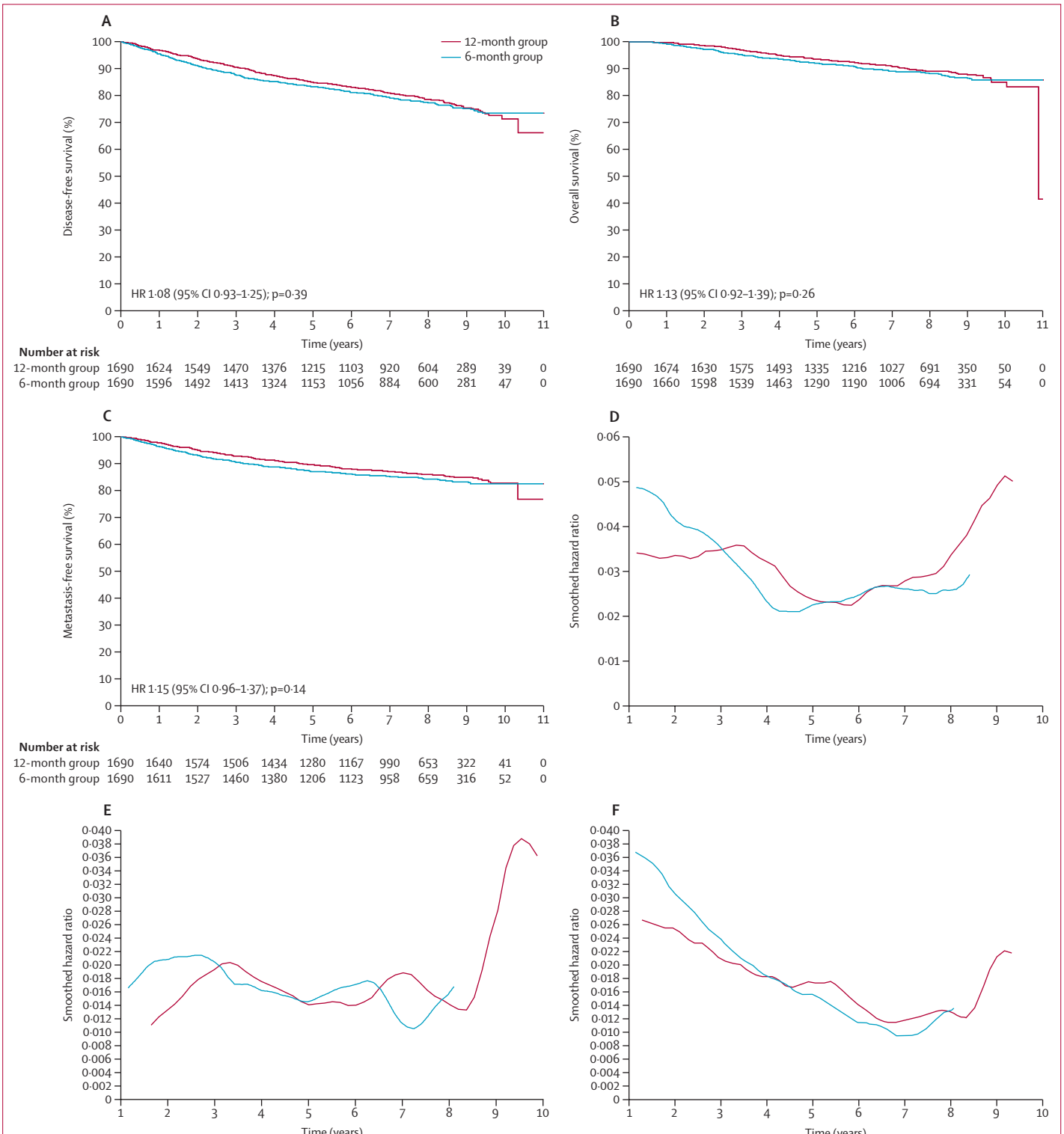

Figure 2: **Disease-free survival (A), overall survival (B), metastasis-free survival (C), and smoothed hazard ratios over time for disease-free survival events (D), overall survival events (E), and metastasis-free survival (F) according to trastuzumab duration**

Disease-free survival (A), overall survival (B), and metastasis-free survival (C) were assessed from the time of randomisation and are adjusted for oestrogen receptor status (positive *vs* negative) and timing of trastuzumab administration and chemotherapy (concomitant *vs* sequential). HR=hazard ratio.

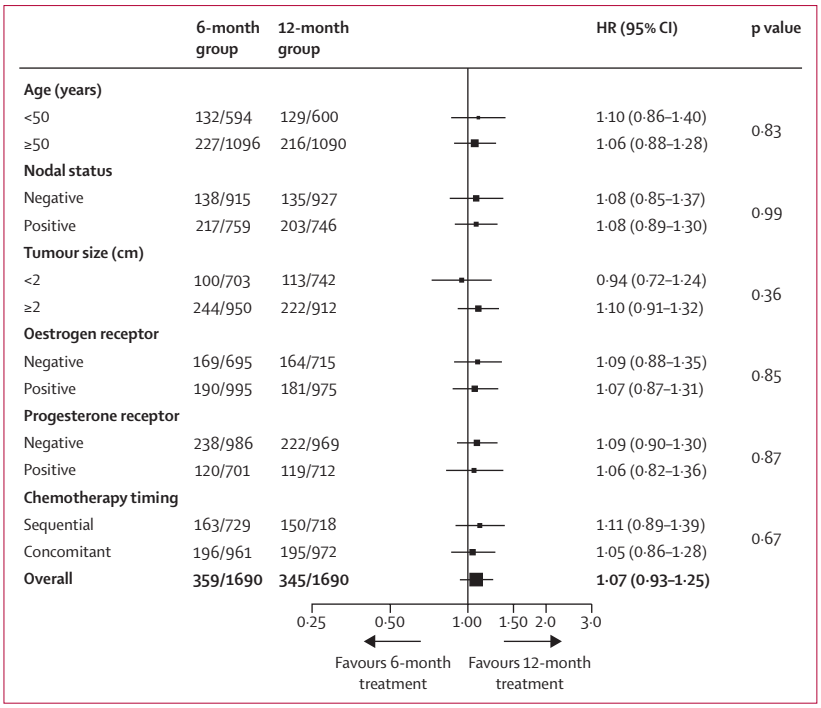

Figure 3: **Univariate forest plot for disease-free survival**
p values are the tests of interaction between treatment and each subgroup, unadjusted for multiplicity. HR=unadjusted hazard ratio.

12-month group and 60 (3·6%) in the 6-month group; 27 (1·6%) contralateral breast cancers in the 12-month group and 33 (2·0%) in the 6-month group; 24 (1·4%) deaths in the 12-month group and 18 (1·1%) in the 6-month group; and 78 (4·6%) second primary malignancies in the 12-month group and 61 (3·6%) in the 6-month group. The HR adjusted for stratification factors was 1·08 (95% CI 0·93–1·25; p=0·39; figure 2A). Since the prespecified non-inferiority margin of 1·15 was included in the CI, the results were inconclusive regarding the non-inferiority hypothesis. The survival estimates in the 12-month group versus the 6-month group were: 92·2% (90·8–93·4) versus 89·3% (87·8–90·7) at 3 years, 86·2% (84·4–87·8) versus 84·2% (82·4–85·9) at 5 years, and 82·3% (80·3–84·1) versus 80·6% (78·5–82·4) at 7 years. Subgroup analyses showed a consistent treatment effect (figure 3).

The proportional hazard assumption of the Cox model was tested based on Schoenfeld residuals, and this assumption was rejected (p=0·004). The graph of smoothed HRs over time supported this non-proportionality (figure 2D). A Cox model including time as a time-dependent covariate enabled the estimation of the HR over the first 2 years. The HR of disease-free survival events over the first 2 years was 1·43 (95% CI 1·12–1·84), indicating that more patients had disease-free survival events early in the 6-month group than in the 12-month group. Another summary of the survival-curve differences was provided by the difference in the RMST (12 months minus 6 months: 0·17 years, 0·2–0·37) and the RMST ratio (12 months over 6 months: 1·02, 1·00–1·04) up to 9·5 years, which favoured the 12-month group.

In the per-protocol analysis, 273 (19·9%) of 1372 patients in the 12-month group and 282 (20·8%) of 1356 in the 6-month group achieved disease-free survival. The estimated HR adjusted for the stratification factors was 1·10 (95% CI 0·93–1·30; appendix p 1).

170 (10·1%) of 1690 patients in the 12-month group and 186 (11·0%) of 1690 patients in the 6-month group died (assessed from randomisation; figure 2B). The estimated HR was 1·13 (95% CI 0·92–1·39). Subgroup analysis revealed a consistent treatment effect. A graph of smoothed HRs over time is shown in figure 2E, and the proportional hazards assumption was rejected (p=0·006).

The distribution of the types of metastasis-free survival events (assessed from randomisation) showed that 224 (13·3%) of 1690 patients in the 12-month group and 249 (14·7%) of 1690 patients in the 6-month group had distant recurrence as the first event; the estimated HR was 1·15 (95% CI 0·96–1·37; figure 2C). Subgroup analysis showed a consistent treatment effect. A graph of smoothed HRs over time is shown in figure 2F; the proportional hazards assumption was rejected (p=0·013).

Overall survival and metastasis-free survival assessed from start of treatment yielded similar results (data not shown).

An exploratory univariate Cox proportional hazards model was used to analyse the primary endpoint disease-free survival, and the secondary endpoints overall survival and metastasis-free survival. Nodal status, oestrogen-receptor status, progesterone-receptor status, and tumour size were significantly related to all three outcomes (data not shown). Additionally, the interaction test in the multivariate model revealed no significant heterogeneity related to the survival endpoints. The estimated HRs adjusted for all previous significant factors and timing of trastuzumab chemotherapy and for the comparison of the 6-month and the 12-month groups were 1·07 (95% CI 0·92–1·24) for disease-free survival, 1·07 (95% CI 0·86–1·32) for overall survival, and 1·13 (95% CI 0·94–1·36) for metastasis-free survival.

After the completion of trastuzumab, few safety events occurred over time. Since our previous publication,[14] no additional cases of heart failure have occurred, and only three cases in which LVEF decreased to less than 50% have been reported in the 12-month group. We found no change in the cardiac safety comparison in this longer follow-up analysis.

Discussion

The first analysis of the PHARE trial in 2012 did not show non-inferiority of 6 months of trastuzumab relative to 12 months in adjuvant treatment of early breast cancer.[9] This first analysis, recommended by the IDMC, included a small number of disease-free survival events, and the heterogeneity of the treatment effect regarding

oestrogen-receptor status and timing of chemotherapy and trastuzumab complicated the interpretation of the findings.[18] This first analysis was inconclusive and did not rule out the possibility that 6 months of adjuvant trastuzumab might be non-inferior to 12 months of treatment. Because the PHARE trial was interrupted by the IDMC at an advanced stage of accrual, the revised statistical plan preserved the opportunity to produce a valid conclusion. The preservation of the initial statistical hypothesis, with an adaptation of the expected number of events due to a refined estimate of disease-free survival (calculated from a longer follow-up of trials with 1 year of adjuvant trastuzumab), allowed for a definitive conclusion.

In this final analysis, the 95% CI included the non-inferiority margin, so the PHARE trial did not find non-inferiority between 6 months and 12 months of trastuzumab. The heterogeneity of the therapeutic effects completely disappeared, confirming the policy of not guiding treatment based on subgroup analyses. In particular, the treatment effect was independent of the timing of chemotherapy and trastuzumab (sequential *vs* concurrent administration). With a longer follow-up, a small number of safety events was reported, and the previously published[9,14] comparison of the safety profiles in the 6-month and 12-month groups did not change. The risk–benefit analysis favoured 12 months of adjuvant trastuzumab for all patients with HER2-positive early breast cancer.

The absence of stringent criteria for defining the acceptable non-inferiority margin complicates the design of such trials and represents an obvious limitation. The non-inferiority margin of 1·15 was chosen in the PHARE trial since an increase of 15% on the HR scale could still be considered acceptable. However, the PERSEPHONE study (NCT00712140),[13] using a similar design with the same clinical endpoint, included a prespecified margin of 1·29 on the HR scale to define non-inferiority. The HRs comparing the 12-month versus 6-month trastuzumab groups are similar in the PHARE study (1·08, 95% CI 0·93–1·25) and in the PERSEPHONE study (1·07, 0·93–1·24). The discordant conclusions are explained by a slightly different statistical prespecified endpoint boundary. If a non-inferiority margin of 1·29 instead of 1·15 had been chosen, non-inferiority could have been claimed in the PHARE trial. These considerations refer more generally to the debate on the determination of the non-inferiority margin. The US Food and Drug Administration guidance[19] on non-inferiority trials, which was issued after the design of the PHARE trial suggests defining a non-inferiority margin to preserve a fraction of the reference treatment effect estimated in historical trials. This approach represents a true improvement in defining non-inferiority and equivalence margins. Nevertheless, the acceptable magnitude of preservation is a subject of debate. The choice of the non-inferiority margin will remain inherently controversial, especially in the context of oncology trials, where the primary outcome is survival and any additional deaths could be considered unacceptable, thereby throwing into question the very feasibility of non-inferiority trials.

Another issue with the PHARE findings is the invalidity of the proportional hazards assumption. The use of the overall HR to compare survival curves and assess the non-inferiority hypothesis might be controversial. In the PHARE trial, the smoothed HRs favoured the 12-month group over the first 2 years, but this benefit seemed to disappear beyond the third year. Non-inferiority of the 6-month versus the 12-month regimen cannot be claimed during the first 2 years, with an estimated HR over this period clearly favouring the 12-month group (1·43, 1·12–1·84). This observation underlines the early benefit of trastuzumab and could dismiss the need for further investigations. The non-proportionality of hazards precludes the use of an overall HR, and another statistical summary is needed. One option would be to consider the survival probability at a specific late timepoint. However, this approach does not capture the profile of events over time. An alternative is to use the RMST to summarise the mean survival time of all patients followed up to 9·5 years. The 0·17-year absolute difference in RMST (0·98 relative difference) represents a 2% relative difference favouring the 12-month group over the 6-month group.

All these statistical considerations consistently favoured the 12-month group, although the difference between groups was small. Without any safety concerns related to adjuvant trastuzumab, a pharmacoeconomic model of the cost savings with a shorter treatment duration seems to be the only criterion supporting a decrease in treatment duration. However, the emergence of biosimilars for trastuzumab will reduce the overall cost and might decrease interest in reducing the duration of trastuzumab treatment.[20–22]

In the PHARE trial, all the statistical investigations favoured the 12-month group. The definitive analyses of the PHARE trial did not show the non-inferiority of 6 months of adjuvant trastuzumab, and 12 months might remain the standard of care. The promising results[23] obtained with trastuzumab-emtansine in the treatment of patients with residual invasive disease after completion of neoadjuvant therapy with a tratuzumab-containing regimen might dramatically change the current treatment strategy in this population. Nevertheless, the conclusions reported by the PHARE and PERSEPHONE trials questioned our ability to address a strategy aimed at reducing therapy duration. The discordant conclusions reached by these studies on the basis of similar results reflect the difficulty in reaching a consensus on acceptable or reasonable differences in efficacy to support a reduction in exposure.

Contributors

XP, IP, GR, PK, PF, and DK designed the study. XP, LG, IP, CF-M, SP-B, JH, and JMG collected the data. XP, JH, SP-B, and JMG did the statistical analyses. XP, GR, MD, J-YP, PK, TB, AL, ME, PF, DS, J-PJ, CJ,

MR, SA-L, LV-B, LC, SC, DK, IP, CF-M, SP-B, JH, and JMG interpreted the results. XP and JMG wrote the manuscript. GR, MD, J-YP, PK, TB, AL, ME, PF, DS, JPJ, CJ, MR, SA-L, LV-B, LC, SC, DK, LG, IP, CF-M, SP, and JH read and reviewed the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

XP has been a consultant for AMGEN, SAMSUNG BioEpis, and Roche, and has received honoraria from Roche; ME and PF have received consultancy honoraria from Roche; CF-M and LG are employed by the sponsor; and IP and DK were previously employed by the sponsor. All other authors declare no competing interests.

Data sharing

Data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others; all available data will be deidentified participant data. The study protocol, statistical analysis plan, informed consent form, and ethics committee approval are available. To access the data, a request should be submitted at the Institut National du Cancer (INCa) with a scientific proposal including objectives. The data will be shared after approval by the INCa and by the steering committee of the PHARE trial. Approval by the ethics committee might be required according to the type of proposal and objectives.

For the **Institut National du Cancer website** see www.e-cancer.fr

Acknowledgments

We thank Andrew Kramar for his input in the statistical analysis in 2013. We thank all patients who gave their consent to be included in the study and the staff of the French INCa for their assistance with all aspects of conducting the trial. We thank the American Journal Expert (Durham, NC, USA) for their support in revising the English.

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