6 versus 12 months of adjuvant trastuzumab in patients with HER2 positive early breast cancer (PERSEPHONE): definitive 4-year disease-free survival results of an open-label, randomised phase 3 non-inferiority trial.

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Short title: PERSEPHONE – Trial of duration of adjuvant Trastuzumab in Early Breast Cancer

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Summary

Background: Adjuvant trastuzumab significantly improves outcomes in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (EBC). The standard duration is 12 months but shorter treatment could provide similar efficacy whilst reducing toxicities and cost.

Methods: We randomly assigned patients with HER2 positive EBC to receive either 6-months or 12-months trastuzumab, in a phase 3 non-inferiority trial. Assuming a 4-year disease-free-survival (DFS) rate of 80% for the 12-month arm, 4000 patients were required to assess the non-inferiority of 6-months (5% 1-sided significance, 85% power), defining non-inferiority as no worse than 3% below the standard arm. A pre-planned, event-driven DFS analysis required 500 events. This trial is registered with EudraCT (2006-007018-39), ISRCTN (52968807), and ClinicalTrials.gov (NCT00712140).

Findings: Between 4th October 2007 and 31st July 2015, 2045 patients were randomised to 12-months trastuzumab and 2043 to 6-months. 69% had ER-positive disease; all patients received chemotherapy (85% as adjuvant treatment); 90% received anthracyclines (48% with taxanes) and 10% taxane-only combinations; 53% had trastuzumab sequentially after chemotherapy. At 5·4 years median follow-up with 335 (8%) deaths, and 512 (13%) DFS events, 4-year DFS rates were 89·4% (95%CI, 87·9-90·7) in the 6-month group and 89·8% (95%CI 88·3-91·1) in the 12-month group (Hazard Ratio 1·07; 90%CI 0·93–1·24, non-inferiority p=0·01), demonstrating non-inferiority of 6-months trastuzumab. Congruent results were found for overall survival (OS) (non-inferiority p=0·001), and landmark analyses 6 months from starting trastuzumab (non-inferiority p=0·02 (DFS) and p=0·02 (OS)). 6-months trastuzumab resulted in fewer patients reporting severe adverse events (373/1939

(19%) versus 459/1894 (24%) 12-month patients, p=0·0002) or stopping early because of cardiotoxicity (61/1939 (3%) versus 146/1894 (8%) 12-month patients, p<0·0001).

Interpretation: We have demonstrated 6-months trastuzumab is non-inferior to 12-months in HER2-positive EBC, with less cardiotoxicity and fewer severe adverse events.

Funding: National Institute for Health Research, Health Technology Assessment Programme (grant number 06/303/98).

Key Words: PERSEPHONE, trastuzumab duration, early breast cancer, HER2 positive, adjuvant therapy.

Introduction

Trastuzumab given with chemotherapy in HER2-positive breast cancer in the metastatic[1] and adjuvant setting[2-4] marked a paradigm shift in treatment with improved outcomes, and longer term follow-up has subsequently confirmed these benefits[5,6]. Twelve months of adjuvant trastuzumab was chosen arbitrarily for the pivotal licensing trials[2-4] and subsequently became standard. However the FinHer trial, which randomised patients to adjuvant chemotherapy with or without 9 weeks concurrent trastuzumab, demonstrated significant improvement in disease-free survival[7] and generated considerable interest in the possibility of shorter trastuzumab durations. Trastuzumab has well-recognised toxicities particularly cardiac[8-11] and significant costs. Studies have been conducted to assess whether similar outcomes can be achieved with reduced treatment duration. PHARE (France)[12], PERSEPHONE (UK)[13] and the HORG study (Greece)[14] compared 6 with 12 months. SHORTHer (Italy)[15], and SOLD (International)[16] compared 12 months with 9 weeks given concurrently with docetaxel-first sequenced chemotherapy, and E2198[17] compared 12 months with 12 weeks given concurrently with weekly paclitaxel. Five of the six de-escalation trials were supported wholly or in part by government funding and aimed to discover the optimal balance between efficacy, toxicity and cost for patients and health services. The PERSEPHONE trial is based on the hypothesis that 6 months adjuvant trastuzumab is non-inferior to 12 months in terms of outcomes, but with reduced toxicity and cost. The trial uses a non-inferiority design [18] and we report 4-year disease-free survival results, the definitive primary endpoint.

METHODS

Study Design and Oversight

PERSEPHONE was a prospective, multicentre, phase 3 randomised trial to test the hypothesis that 6 months of trastuzumab therapy is non-inferior to 12 months. The trial was approved by the Multi-Centre Research Ethics Committee (07/MRE08/35), Local Research and Development Departments at participating institutions, was sponsored by Cambridge University Hospital NHS Trust and University of Cambridge and co-ordinated and analysed by the Warwick Clinical Trials Unit at the University of Warwick. The trial was conducted in accordance with the Declaration of Helsinki, supported by the National Cancer Research Network (NCRN No 4078), and funded by the National Institute for Health Research (NIHR) Health Technology Assessment Programme (HTA), grant number 06/303/98. The trial recruited patients in 152 centres in the UK, under the auspices of an Independent Data Safety and Monitoring Committee (IDSMC), an Independent Trial Steering Committee (TSC), and a Trial Management Group (TMG).

Participants

Eligible patients, 18 years or older, had a histological diagnosis of invasive EBC with overexpression of HER2 receptor defined according to the ASCO/CAP Guidelines[19]. All patients had a clear indication for chemotherapy and at the start of the trial, following written informed consent, were randomised prior to starting trastuzumab. However, in 2009 recruitment rate remained substantially lower than expected and after discussion between the TMG, TSC, IDMSC and funders, a protocol amendment (Protocol v.3.1 July 2009) allowed randomisation to occur at any time up to and including the ninth cycle of

trastuzumab. All participants were considered medically fit to receive treatment by the responsible clinician. Female patients who were of child-bearing potential were non-pregnant, non-lactating, and agreed to use adequate contraception during treatment.

Randomisation and masking

The trial was open label and patients were randomised (1:1) to either 12 months (standard - 18 cycles) of trastuzumab or 6 months (experimental - 9 cycles) of trastuzumab (Figure 1). Randomisation was performed by telephone to the Warwick Clinical Trials Unit, where a central computerised minimisation procedure used the following stratification variables; oestrogen receptor (ER) status (positive: negative); chemotherapy (CT) type (anthracycline (A) without taxane (T): A with T: T without A: neither A nor T); CT timing (adjuvant (ACT): neoadjuvant (NACT)); and trastuzumab timing (concurrent: sequential).

Procedures

Trastuzumab was administered every 3 weeks either intravenously (IV) or, following a protocol amendment (https://warwick.ac.uk/fac/sci/med/research/ctu/trials/cancer/persephone/professionals Version 4·0: 31st October 2013), sub-cutaneously (SC). Switching from IV to SC was allowed at clinician discretion. The IV loading dose was 8mg/kg followed by maintenance doses of 6mg/kg, and the SC dose was fixed at 600mg.

After randomisation, patients were followed-up routinely at the centre where the patient was recruited or an associated institution with ethical approval for the study. Follow-up was every 12 weeks for the first year after starting trastuzumab, recording all toxicities experienced. Common Toxicity Criteria Adverse Events (CTCAE version 3) grades were recorded for each trastuzumab cycle after randomisation. Originally, 3-monthly left ventricular ejection fraction (LVEF) assessments for up to 12 months after starting trastuzumab were required in all patients. However in June 2013, the IDSMC recommended reducing LVEF monitoring to 4-monthly, in line with new national guidelines[20]. Trastuzumab was discontinued if LVEF fell below 50%, and then LVEF was re-checked after 6 and then 12 weeks. Trastuzumab was restarted with recovery of LVEF, however if treatment could not be restarted for 12 weeks because of persistently low LVEF, it was stopped permanently. Follow-up was carried out 6-monthly for the second year and annually thereafter, in accordance with standard local practice and continued for 10 years.

Outcomes

The primary endpoint of DFS was calculated from the date of diagnostic biopsy to date of first invasive breast cancer relapse (local or distant) or death, or to date of censor in patients alive and relapse-free. Overall survival (OS) was also calculated from the date of diagnostic biopsy. Additional analyses of disease-free interval (DFI), distant DFI (DDFI), distant DFS (DDFS), invasive DFS (IDFS) (including contralateral breast and second primary cancers - IDFS according to the STEEP system[21]), and breast-cancer specific survival (BCSS) were carried out. Since randomisation could occur at any time up to and including the ninth cycle of trastuzumab, a landmark analysis was carried out from 6 months after the start of

trastuzumab. The number of trastuzumab cycles received per patient was recorded, with route of administration and reasons for any deviation from protocol. LVEF measurements were defined as low if results were <50% or reported as low without quantification of LVEF. Incidence of clinical cardiac dysfunction, defined as symptoms or signs of congestive heart failure or new cardiac medication, was recorded every 3 months for 12 months. A cardiologist (CP) was a member of the trials group and reviewed the cardiac toxicity together with the CI (HME) and other members of trial management group.

The Quality of Life assessment schedule specifies assessments before starting trastuzumab, and then 3, 6, 9, 12, 18 and 24 months later. All patients followed this schedule from the time they entered the trial, completing assessments at the same time-points in their treatment but, if randomised part way through their trastuzumab treatment, with the omission of the missed baseline +/- 3-month time-point. Questions regarding general health and the EuroQoL EQ-5D-3L were recorded. Health economic analysis will be reported separately.

Statistical Analysis

The trial was designed to assess non-inferiority of the experimental group (6 months trastuzumab), and the clinically acceptable non-inferiority margin for the 6 month group was defined as being not worse than 3% absolute below the 4-year DFS of the standard group (12 months trastuzumab). This 3% non-inferiority margin was decided before the start of the trial following consensus from the trial development group together with the patient and public involvement group. Data from adjuvant trastuzumab trials at the time[2-4]

estimated the 4-year DFS for patients treated with 12 months trastuzumab to be 80%. Consequently, 4000 patients (2000 in each group) were required to demonstrate the non-inferiority of 6 months' trastuzumab with a 3% non-inferiority margin of the 4-year DFS, with 5% 1-sided significance, and 85% power. This assumes a 4-year recruitment period, an additional 5 years follow-up and 4% lost-to-follow-up rates. Survival curves were plotted using Kaplan-Meier methodology and the hazard ratio (HR) between the two arms was estimated using a Cox's proportional hazards model containing only the trial treatment effect, after graphical checks for proportionality of hazards. The upper limit of the HR required to demonstrate the 3% non-inferiority was only to be calculated at the time of analysis, and based on the DFS in the 12-month arm observed at the time of analysis. As described in Mauri and D'Agostino [22] if the upper limit of the 90% confidence interval (the 95th percentile) of the estimated HR was less than the relevant 3% absolute non-inferiority limit, then the experimental group (6-months trastuzumab) would be regarded as non-inferior.

Warwick Clinical Trials Unit carried out all analyses using SAS v9·4 software. The IDSMC approved statistical analysis plan (SAP) stated that the event-driven primary endpoint analysis required 500 DFS events to have occurred. At this point, the relevant non-inferiority limits in terms of HR for 3% non-inferiority in DFS were calculated using the observed 4-year DFS rates in the standard, 12-month group. The SAP included a secondary analysis adjusting for stratification and baseline prognostic factors and also the presentation of treatment effect on DFS for each stratification variable using hazard ratio plots[23]. To remove the effect of timing of randomisation, the SAP also defined an exploratory landmark analysis for

patients alive and disease-free 6 months after starting trastuzumab. All randomised patients were included in all analyses where possible and were analysed on an intention-to-treat (ITT) basis since the trial aimed to compare durations of trastuzumab in routine clinical practice. PERSEPHONE is registered with EudraCT (2006-007018-39), ISRCTN (52968807), and ClinicalTrials.gov (NCT00712140).

Role of the funding source

The funder of the study (NIHR HTA) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data and, along with LH and JD, had final responsibility for the decision to submit for publication with the agreement of all the authors and the data monitoring and safety committee. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

RESULTS

A total of 4089 patients were randomised by 210 clinicians at 152 sites in the UK between 4th October 2007 and 31st July 2015. One double randomisation reduced the analysis set to 4088 patients (Figure 1). Nineteen patients were deemed ineligible (7, 12-month patients: 12, 6-month patients), principally for previous cancers or DCIS treated by radiotherapy as well as surgery. Patient characteristics including minimization and other prognostic variables were balanced across the two groups (Table 1). Sixty-nine percent of patients had ER positive tumours; 58% of ACT patients were node negative, and 47% of ACT patients had tumours <2cm. Randomisation before the start of trastuzumab occurred in 44% of patients and the timings for those randomised after the first cycle of trastuzumab are shown in appendix p1. Among NACT patients (n=620), 89% received A and T, 9% A without T, 2% T without A; corresponding percentages for ACT (n= 3468) were 41%, 48% and 11% (appendix p1). UK standard practice gradually changed during trial recruitment with a steady increase in anthracycline and taxane combinations, trastuzumab commencing concurrently with taxanes but not anthracyclines, taxane-based treatment without anthracyclines and neoadjuvant timing (appendix p2). Patients given trastuzumab and chemotherapy concurrently compared with sequentially were more often node positive (53% and 32% respectively), had larger tumours (> 2cms: 55% v 47% respectively), received neoadjuvant treatment (26% v 6% respectively) and in addition had shorter median duration of follow-up (4·5 years v 5·8 years) (appendix pp2-5).

Complete trastuzumab administration details are available for 3836/4088 (94%) patients; 93% 12-month patients and 95% 6-month patients (Figure 1). Eighty-two percent

(40,530/49,632) of trastuzumab cycles were administered IV and 18% (9,102/49,632) SC. In total 3294/3836 (86%) patients received the protocol specified number of trastuzumab cycles; 1556/1895 (82%) 12-month patients and 1738/1941 (90%) 6-month patients. The most common reasons for early treatment cessation were cardiac toxicity (146/1894 (8%) 12-month patients, 61/1939 (3%) 6-month patients) and patient request (91/1894 (5%) 12-month patients, 24/1939 (1%) 6-month patients). Delays occurred in 3631/49,632 (7%) cycles (appendix p4), the main reasons being holidays (n=827 (23%)), sepsis/infection (n=184 (5%)) and cardiotoxicity (n=178 (5%)). The commonest chemotherapy treatments (known for 3959 patients), were fluorouracil, epirubicin, cyclophosphamide, with docetaxel (FEC-T) (12-month: 811/1985 (41%); 6-month: 790/1974 (40%)) and FEC (12-month: 548/1985 (28%); 6-month: 567/1974 (29%)).

At database lock on 17 April 2018, with a median follow-up of 5·4 years (IQR 3·6-6·7 years) and 96% of alive patients followed up for at least 2 years, 335 deaths (8% of the 4088 patients) had been reported, 81% due to breast cancer (Table 2). Local or distant relapse occurred in 452 (11%) patients, with distant metastases (373 patients) occurring in the liver (160 patients (43%)), bone (142 patients (38%)), lung (139 patients (37%)), and brain (78 patients (21%)). A relapse or death was reported for 512 patients (13%).

The 4-year DFS rate in the 12-month group was 89·8% (95% confidence interval (CI) 88·3-91·1) and 89·4% (95% CI 87·9-90·7) in the 6-month group (Figure 2A). Thus, with the non-inferiority margin of 3%, the non-inferiority limit for the hazard ratio (HR) was set at 1·32. The HR for relapse or death with 6 months compared to 12 months trastuzumab was 1·07

(90%CI 0·93, 1·24); this outcome met the pre-specified definition of non-inferiority (non-inferiority p=0·01). The two-sided p-value for difference between treatments was 0·42. Adjustment for all stratification factors gave the same results with a HR of 1·07 (90%CI 0·93, 1·24; non-inferiority p=0·01). Analysis of OS (Figure 2B) also met the pre-specified definition of non-inferiority (4-year OS rate of 94·8% in the 12-month group, HR non-inferiority limit 1·60, HR=1·14 (90%CI 0·95, 1·37), non-inferiority p=0·001). The two-sided p value for difference between treatments was 0·22, and adjusting for stratification factors found similar results (HR=1·13 (90%CI 0·94, 1·35)).

Forest plots for DFS including all patients (Figure 3A) showed heterogeneity for chemotherapy type (p=0·01) predominantly driven by the small number of events in the taxane-only group, in which most patients received docetaxel with cyclophosphamide [25]. The timing of trastuzumab relative to chemotherapy (concurrent/sequential) showed heterogeneity (p<0·001) favouring 12 months in patients receiving concurrent trastuzumab. Forest plots for OS (appendix p6) again showed heterogeneity for concurrent and sequential patients; they additionally showed heterogeneity for ER status (p=0·02), with patients with ER negative disease appearing to do better with 12 months trastuzumab. . No heterogeneity was observed for age, grade, menopausal status or IHC 3+:IHC2+/FISH positive in DFS or OS. Exploratory forest plots for adjuvant patients only (Figure 3B and appendix p7) showed similar results, with no heterogeneity for node status, size, and combined ER and node status.

The landmark analysis of DFS and OS included 4009 patients who remained alive and disease-free 6 months from starting trastuzumab. Similar results were found both for the landmark DFS (HR=1·07 (90%CI 0·92–1·24) non-inferiority p=0·02) and OS (1·13 (90%CI 0·94–1·37) non-inferiority p=0·02) analyses (Figure 4). Congruent results were found for DFI, DDFI, DDFS, IDFS, and BCSS analyses (data not shown). Forest plots for landmark DFS and OS also showed similar results to those observed for DFS and OS (appendix pp8-11).

During the 12-month period from starting trastuzumab a higher proportion of 12-months patients than 6-month patients reported at least one adverse event of severe grade (CTCAE>=3, or 2 for palpitations; 459/1894 (24%) vs 373/1939 (19%) respectively, p=0·0002) (Table 3). The excesses were in cough (4·3% v 2·3%: p=0·0005), palpitations (4·8% v 2·7%: p=0·0007), fatigue (11·9% v 8·6%: p=0·0009), pain (5·2% v 3·2%: p=0·003), chills (3·5% v 2·1%: p=0·008), muscle/joint pains (11·4% v 9·0%: p=0·02), and nausea (1·8% v 1·0%: p=0·05) (appendix p12). These were seen predominantly during the 7-12 month period. Similarly, the number of serious adverse reactions (SARs) reported were 67 occurring in 64 12-month patients and 34 occurring in 29 6-month patients, the excesses seen during the 7-12 month period. Clinical cardiac dysfunction was reported more commonly in 12-month than 6-month patients (224/1968 (11%) vs 155/1994 (8%) respectively, p<0·0001) (Table 3). A small absolute difference was observed in the first 6 months (8% of 12-month patients, 6% of 6-month patients, p=0·02), with a larger difference during the 7–12-month period (8% vs 5% respectively, p=0·0002). Trastuzumab was stopped early because of cardiac toxicity in 146/1894 (8%) of 12 month patients and 61/1939 (3%) of 6 month patients (p<0·0001).

In total, 19,414 measurements of LVEF were made in 4078 patients; 10162 on 2040 12-months patients and 9252 on 2038 6-month patients. During the first 6 months of treatment, proportions of patients with low LVEF were 7% in both groups (p=0·96). However, during months 7–12 this proportion increased for 12-month patients (8%) but fell for 6-month patients (5%) (p=0·0003 for difference between groups). During months 7 to 12, significant falls of LVEF to <50% after a baseline of >=59% occurred in 4% of patients in the 12-month and 2% of patients in the 6-month group (p=0·001). Eleven deaths were considered cardiac (primary or contributory cause) however none occurred during trastuzumab and none were considered to be related to trastuzumab by the TMG (appendix p5). Comparing the 44% of patients randomised into the trial before the start of trastuzumab with all patients, the comparisons of toxicity between the two arms was broadly similar, although toxicity including cardiotoxicity showed marginally higher rates for both 6 and 12 months for patients randomised before the start of trastuzumab, (appendix p 6).

In total, 3910 patients (1960 12-month patients, 1950 6-month patients) participated in the QoL sub-study. In both groups, feelings of general health are seen to decline during the first three months of trastuzumab (appendix p14), when 47% of patients will have been receiving concurrent chemotherapy, and then steadily improve after completion of treatment. The EQ-5D-3L health state is seen to remain steady from baseline to three months for both randomised groups, with a trend to slowly increasing after this, occurring slightly later for 12-month patients (appendix p15).

DISCUSSION

Adjuvant trastuzumab in HER2-positive EBC has improved the long-term outcome for this poor prognosis molecular subtype[27], and twelve months treatment is currently the standard duration. In 2006, the FinHER trial[7] demonstrated efficacy for a significantly shorter duration (9 weeks) compared with a no trastuzumab control arm and on the strength of this study the PERSEPHONE Trial was designed to test 6 months of trastuzumab against the standard duration of 12 months. Using an established design[18], PERSEPHONE has demonstrated non-inferiority for 6 months of trastuzumab compared with 12 months. Our definition of non-inferiority was no worse than 3% absolute below the standard group's 4-year DFS rate, and the non-inferiority limit was thus calculated as a hazard ratio (HR) of <1·32. Notably, the upper confidence limit of the HR was 1.24, which is significantly below this non-inferiority boundary. This reflects, that although the non-inferiority boundary was set at 3%, the actual point estimate reduction observed was very small at 0.4% for 4-year DFS and 0.1% for the landmark 4-year DFS. Other outcome analyses including OS, landmark OS 6 months after the start of trastuzumab, and sensitivity analyses for other survival endpoints were all congruent, demonstrating the non-inferiority of 6-months treatment. In addition, cardiac and other toxicities were reduced with 6-months treatment and therefore the balance of risk and benefit favours shorter treatment. It must be recognised that the patient population in PERSEPHONE, mapping onto standard practice in the clinic, had a significantly better profile of standard prognostic factors than patients treated in the original adjuvant trastuzumab trials[2-5]. The trial included 69% patients with ER-positive tumours compared with 36-54% in registration studies; 58% patients were node negative compared with 7-33%; and 47% had tumours ≤ 2cms compared with 35-40%. These standard prognostic factors are

similar to those for patients entered into PHARE and the other non-inferiority trials. PERSEPHONE recruited the number of patients specified in the statistical plan and with an event-driven analysis was sufficiently powered to meet the primary endpoint. PERSEPHONE is the largest trastuzumab duration comparison carried out in early breast cancer and the only one to demonstrate non-inferiority for the primary endpoint of reduced duration adjuvant trastuzumab.

Prior to the set-up of the trial there was consensus from the PERSEPHONE TMG and the patient and public involvement (PPI) group, that an absolute difference up to 3% for the 6-month treatment was considered acceptable by clinicians and patients. This is a margin commonly used in non-inferiority trials in oncology, including the recently published TAILORx study[28]. Approval for the trial from funders (NIHR HTA) with national and international peer-review, National Research Ethics Committee (REC) and each recruiting centre, endorsed the view that demonstrating this non-inferiority margin would be important, and if proven would be potentially practice changing. In the PERSEPHONE statistical analysis plan, we planned to calculate the HR limit of non-inferiority using the observed 4-year DFS in the standard arm at the time of the primary endpoint analysis. This statistical analysis plan was approved by the IDMSC as most appropriate for the study.

Two other randomised studies compared 6 with 12 months, the HORG[14] and PHARE[12] trials. The HORG[14] study included only 481 patients and employed a non-inferiority margin of 8% using dose-dense FEC followed by docetaxel as chemotherapy with 6 or 12 months trastuzumab commencing concurrently with docetaxel. This relatively small trial did not

demonstrate non-inferiority for 3-year DFS. The PHARE Trial[12] had an original recruitment target of 7,000 patients with a 2% non-inferiority margin. The trial included fewer patients than originally planned (n=3384) and reported an early primary endpoint of DFS at 2 years on the advice of the IDMSC. The HR non-inferiority limit was pre-specified at 1·15 on the expected standard arm DFS rate at 2 years of 85%. The trial reported a HR of 1·28 (95% CI 1·05–1·56; non-inferiority p=0·29) and therefore failed to show non-inferiority. The longer term results from PHARE were very recently presented[29] after a median of 7.5 years and the HR was 1·08 (95%CI, 0·93-1·25: non-inferiority p=0·39) with the upper confidence limit still exceeding the HR limit of 1·15. Therefore, the conclusion remained the same: non-inferiority was not confirmed. However the HR is now remarkably similar to that seen in the PERSEPHONE trial. The PERSEPHONE and PHARE Trials Groups established a collaboration at the start of the trials for an individual-patient data meta-analysis / joint analysis, which will provide larger numbers for exploratory subgroup analyses.

Long term follow-up of patients within the PERSEPHONE trial is planned. The importance of this in trials of HER2 positive breast cancer has been emphasised by a number of studies in which results have changed with longer follow-up. The PHARE Trial[29] report after over 7 years of follow-up shows a significant reduction in the HR for disease recurrence or death of 6 months trastuzumab (HR 1.08) when compared with the 2 year results (HR 1.28). In contrast the FinHer study which provided the stimulus for all the reduced duration trials, demonstrated with longer follow up[30] less effect in terms of the HR for disease recurrence or death which increased from 0.42 at 3 years, to 0.65 with a median follow-up time over 5 years. In addition, a recent presentation from a combined analysis of the N9831 and NSABP

B31 studies[31], shows that the risk of recurrence after 5 years is higher in ER+/HER2+ than ER-/HER2+ disease and this is relevant for PERSEPHONE because of the inclusion of a high percentage of ER positive patients. Longer follow-up in the PERSEPHONE Trial will also be particularly important because changes in standard treatments during the trial mean that for concurrent, anthracycline with taxane-based, and neoadjuvant treatments there will be on average shorter follow-up for these subgroups of patients.

Two trials tested 9 weeks concurrent treatment versus 12 months and neither demonstrated non-inferiority. SHORTHer[15] randomised 1253 patients, the non-inferiority limit for a <3% margin below standard treatment was HR<1·29 for the primary endpoint of DFS at 5 years and the trial HR was 1·15 (90%CI 0·91, 1·46). SOLD[16] randomised 2176 patients, the non-inferiority limit for a <4% margin was HR<1·385 for the primary endpoint of DFS at 5-years and the trial showed HR was 1·39 (90%CI 1·12-1·72). One potential explanation is that the total dose of trastuzumab in the 9-week group is 20mg/kg which is significantly less than the 56mg/kg in PERSEPHONE, PHARE and HORG. This total dose may be insufficient to produce a non-inferior outcome compared to 12 months, even when used concurrently with docetaxel and sequenced immediately after surgery.

Heterogeneities between pre-specified stratification subgroups are seen in the PERSEPHONE Trial. For DFS there is apparent heterogeneity (p<0·001) for timing of trastuzumab and chemotherapy; patients receiving concurrent treatment appeared to benefit more from standard 12 months trastuzumab. This is an intriguing result since we anticipated that concurrent rather than sequential timing of trastuzumab and

chemotherapy would demonstrate non-inferiority because of evidence of synergy of concurrent treatment from in vitro data[32], and metastatic[1] and adjuvant[7,12,33] clinical trials. At the present time our demonstrated heterogeneity for trastuzumab scheduling and duration cannot be readily explained, but it is important to note that the decision to use concurrent or sequential treatment was selected by investigators and not randomised. Given that patients treated with concurrent chemotherapy also generally had more high risk features, it is not clear whether the observed heterogeneity is due to the treatment schedule per se, the type of chemotherapy used or whether it reflects the underlying risk of relapse. However, although the trial was stratified by concurrent and sequential chemotherapy and subgroups are balanced in terms of numbers of patients receiving either 6 or 12 months trastuzumab, these groups are smaller, and therefore lack statistical power. All patients in the concurrent group received either anthracycline and taxane combinations or taxane based chemotherapy without anthracyclines. HERA [2,34] is the only trial reporting data for an exploratory subgroup analysis of a non-randomised comparison of sequential administration of trastuzumab after anthracycline and taxane, with trastuzumab after anthracycline without taxane chemotherapy. There is an interesting trend for less effect of trastuzumab in the anthracycline and taxane group, although this does not reach statistically significant levels of interaction. Whilst we acknowledge that any possible interaction between concurrent and sequential trastuzumab with chemotherapy may raise some concern, it is to be remembered that this subgroup analysis lacks statistical power for non-inferiority. The heterogeneity demonstrated for different chemotherapy backbones is driven mainly by the taxane without anthracycline group and this result should be interpreted with caution given the small size of this group and the very small number of events. For OS, heterogeneity is demonstrated in addition for ER status (p=0·02); patients

with ER negative disease appeared to benefit more from 12 months trastuzumab which is perhaps not surprising given the increased risk of relapse in this group.

PERSEPHONE mapped onto standard practice in the UK and study strengths are broad inclusion criteria, which allowed recruitment of a large number of patients in routine clinics and ongoing recruitment as standard chemotherapy regimens and trastuzumab timing changed. The limitations of this design include the potential for complex interactions between trastuzumab duration and prognostic factors, the changing standard practice over the 8 years of the trial, the variable timing of randomisation potentially introducing ascertainment bias and selection of chemotherapy and trastuzumab timing according to perceived risk by the investigators i.e. concurrent preferred in higher risk patients (appendix pp2-4). An additional limitation that must be borne in mind is that the analyses were performed according to the intention-to-treat principle. While we believe that this is the most appropriate to use, ensuring unbiased estimates, it can potentially underestimate differences between treatment arms and thus drive the results towards non-inferiority. This is a concern particularly when adherence to treatment is low and/or differential loss to follow-up occurs. In that respect within the PERSEPHONE Trial, adherence to protocol-mandated treatment is high and loss to follow-up is low.

All reduced duration trastuzumab trials have demonstrated less cardiotoxicity for the shorter duration[11,15,16]. In addition, the HERA trial showed that 24 months of trastuzumab further increased rates of cardiotoxicity without improving cancer outcomes[5,9]. As part of the translational programme in PERSEPHONE over 80% of patients have donated blood

samples which will be part of a genome-wide association study of cardiotoxicity with investigation of interaction with duration of treatment.

There have been significant changes to the management of HER2 positive early breast cancer over the past 13 years since neo/adjuvant trastuzumab was introduced and the concept for the PERSEPHONE trial was developed alongside the other duration trials. The trial was designed to be pragmatic, map onto standard practice, which allowed patients to continue to be enrolled as standard chemotherapy regimens and trastuzumab timings changed. Whilst this is an advantage for trial recruitment and ensures contemporaneity, one of the limitations of this design is that there will not be sufficient power in different subgroups to confirm non-inferiority. Following the report of N9831 in 2011 [33] which demonstrated superiority of concurrent trastuzumab and taxane chemotherapy over sequential trastuzumab, there was increasing use of concurrent treatments. Up until 2011, the majority of patients in the UK received standard anthracycline-based regimens with sequential trastuzumab similar to those used successfully in HERA [2]. The TCH (docetaxel, carboplatin, Herceptin) regimen from the BCIRG 006 study [4] and the APT (adjuvant paclitaxel and trastuzumab) [37] which avoid anthracyclines are now widely used in North America and are gaining in acceptance in Europe including the UK. The APT regimen was developed in particular for low risk node negative patients and tested in a phase II non-randomised study. Our study includes only 403 (10%) patients, entered more recently, who received non-anthracycline containing regimens andin whom there have been very few events; therefore no conclusions can be drawn about the effect of a shorter duration in combination with a non-anthracycline regimen.

There have been additional advances in the management of HER2 positive early breast cancer which warrant consideration. Trials of neoadjuvant therapy can provide personalised HER2 directed therapies with potential for both escalation and de-escalation strategies. There has been increasing use of dual anti-HER2 therapy (trastuzumab and pertuzumab) with chemotherapy in the neoadjuvant setting following the Neo-SPHERE trial [38,39], which showed improved pCR rates and disease-free survival. In the recently published Katherine Trial [40], trastuzumab emtansine (TDM-1) was tested against trastuzumab after failure of neoadjuvant chemotherapy and anti-HER2 therapy to produce a complete pathological response (pCR). The estimated percentage of patients who were free of invasive disease at 3 years was 88.3% in the T-DM1 group and 77.0% in the trastuzumab group. Invasive disease–free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95% confidence interval, 0.39 to 0.64; P<0.001) [40]. This significant improvement in outcomes is likely to lead to an appropriate escalation of standard treatment in the post-neoadjuvant setting, at least for patients who do not achieve pCR with neoadjuvant treatment. On the other hand, patients who do achieve a pCR could be considered for trials which are planned for de-escalation of HER2 therapy. The APHINITY trial reported improved outcomes for the addition of 12 months adjuvant pertuzumab to 12 months trastuzumab. The reduction in disease recurrence was relatively small, albeit statistically significant[35] (HR, 0·81; 95%CI 0·66-1·00; p=0·045) and subgroup analysis showed a larger effect for the node-positive subgroup. More precise prognostic/predictive classification is urgently required[36] in order that the results of the de-escalation trials and those escalating treatment with dual HER2 therapy[35] can be appropriately applied to optimise effectiveness whilst reducing toxicity and containing cost. As part of the translational research programme within the PERSEPHONE trial over 80% of

patients have donated formalin-fixed paraffin embedded tumour tissue and germline bloods, and our aim is to investigate personalising trastuzumab duration taking into account germline and tumour genomics, as well as efficacy, toxicity and standard prognostic factors.

In general, there remain very significant challenges to de-escalating effective treatments that have been used as standard for many years. There is likely to be an understandable reluctance on the part of both oncology teams and their patients to consider a change to practice which has been established since 2005, despite the potential benefit for the individual patient of reduced toxicity, length of treatment and a more rapid return to normal life. As we report the results of the PERSEPHONE trial, and reflect on the progress of our study from original concept to the present day, we are convinced that the optimal time to evaluate shorter durations is in registration trials, and we would strongly encourage such testing for new targeted adjuvant cancer therapies. Although we have demonstrated non-inferiority for trastuzumab in the population we tested, there is ongoing discussion and intense debate about our results, including whether or not these are applicable in 2019 as compared with 2007 when the study was designed, due to the changes in standard treatments for HER2 positive breast cancer that have occurred. Duration questions within registration trials could only occur with significant high level international collaboration between the pharmaceutical industry, international academic groups, governments / medicines approval bodies such as the EMEA and FDA, with input from the wider cancer specialist teams and cancer patients, as has been discussed by Martine Piccart and her colleagues[41]. If shorter treatments are found to be non-inferior by agreed statistical criteria at the outset then these will become the standard of care on licensing. The escalating cost of effective novel anti-cancer treatments is rapidly becoming unsustainable even for

wealthy nations, and we believe clinical trials designed to test the non-inferiority of shorter treatments should become one of the priorities in cancer research.

In conclusion, in the PERSEPHONE trial, we have demonstrated non-inferiority for 6 months adjuvant trastuzumab compared with 12 months in HER2-positive early breast cancer in the population treated. The observed absolute difference in the primary endpoint of DFS at 4 years was only 0·4%. This result signals the potential of reducing treatment duration to 6 months and thereby toxicity and cost whilst producing similar efficacy for at least some women with HER2 positive breast cancer. This trial provides a positive result and will stimulate significant debate since it is the only reduced duration study to demonstrate non-inferiority for shorter adjuvant trastuzumab.

RESEARCH IN CONTEXT

Evidence before the Study

The benefit of adjuvant trastuzumab in HER2 positive breast cancer was established in 2005 with the publication of two pivotal registration trials which both used 12 months trastuzumab and chemotherapy, compared with chemotherapy alone. Both HERA and a joint analysis of NSABP-B31 and NCCTG-N9831 demonstrated a significant improvement in disease-free survival (DFS). Shortly afterwards in 2006 the smaller FinHER trial (231 patients) published similar results for just 9 weeks trastuzumab given concurrently with docetaxel as the first definitive adjuvant treatment. This result prompted significant interest in de-escalation trials to establish whether shorter duration trastuzumab could have similar efficacy. PERSEPHONE, PHARE and HORG tested 6 months against the standard 12 months, and SOLD and SHORTHer tested 9 weeks (given in a similar way to the FinHer protocol) versus 12 months.

Added Value of this Study

The Persephone Trial mapped onto standard practice in the UK and accepted patients who were planned to receive adjuvant trastuzumab and chemotherapy. Patients were randomised to 6 versus 12 months trastuzumab. The trial has a non-inferiority design and, with recruitment of 4088 patients, was powered to test that 6-months was no worse than 3% below the standard disease-free survival (DFS) with 12 months treatment. Analysis following 512 DFS events showed a 4 year DFS of 89·4% with 6-months treatment and 89·8% with 12 months treatment. HR was 1·07 (90%CI 0·93–1·24, non-inferiority p=0·01) demonstrating non-inferiority for 6-months treatment. Persephone is the largest of the

reduced duration, adjuvant trastuzumab trials which recruited the required number of patients and accrued the number of events set out in the statistical analysis plan. This is the only trial to demonstrate non-inferiority in HER2 positive early breast cancer.

Implications of all available evidence

Available evidence for trastuzumab duration includes the SOLD and SHORTHer trials comparing 9 weeks trastuzumab to 12 months. Neither were able to demonstrate non-inferiority, however, it is possible that 9 weeks trastuzumab is not a long enough duration to provide the benefit in outcomes seen with 12 months treatment. The smallest of the three trials comparing 6 months trastuzumab with 12 months was the 481-patient HORG trial which failed to demonstrate non-inferiority at the 8% level (HR=1·58 (95%CI 0·86-2·90). The 3380-patient PHARE trial initially reported in 2013, and did not demonstrate non-inferiority at the 2% level (HR=1·28 (95%CI 1·05-1·56)). However, this trial was recently presented with longer follow-up and results showing a HR of 1·08 (95%CI 0·93-1·25) which are remarkably similar to the 4088-patient PERSEPHONE's findings (HR=1·07 (90%CI 0·93-1·24). During the time the trial recruited over 8 years there were changes in standard practice supported by randomised evidence which included use of trastuzumab concurrently with chemotherapy rather than sequentially and the introduction of non-anthracycline based chemotherapy from BCIRG 006. There was also non-randomised evidence for non-anthracycline de-escalated chemotherapy in better risk patients (APT and docetaxel / cyclophosphamide). During the trial standard treatments gradually changed in the clinic. PERSEPHONE demonstrates non-inferiority for 6 months trastuzumab in the early disease setting and we believe this result should signal the possibility of reduced duration trastuzumab in HER2

positive patients. However, the study does not have the statistical power to address the duration question for any specific chemotherapy regimen or sub-group.

DATA SHARING

Data collected within the PERSEPHONE study will be made available to researchers whose full proposal for their use of the data has been approved by the Persephone Trial Management Group and whose research group includes a qualified statistician. The data required for the approved, specified purposes and the trial protocol will be provided, after completion of a data sharing agreement. Data sharing agreements will be set up by the sponsors of the trial, the funders, the trial coordination centre, and the Trial Steering and Management Groups. The data will be made available 2 years after publication. Please address requests for data to:

persephone@live.warwick.ac.uk

Contributors

HE, LH, A-LV, DM, AW,DC and JD contributed to conception. HE, LH, A-LV, CM, CH, DM, AW, DC and JD contributed to grant writing. HE, LH, A-LV, MW, CP, JM, BM-A, EP, CM, CH, DM, AW, DC and JD contributed to the study design. HE, LH, A-LV, SL, DH, HH MW, BM-A, EP, AC, CM, CH and JD contributed to the study set-up. HE, LH, A-LV, SL, HH, DC and JD contributed to the oversight of trial conduct. HE, LH, A-LV, SL, KM, LH-D, AH, DR, KR, MW, CP, JM, JA, CC, PH, CM, CH, DM, AW, DC and JD were members of the Trial Steering Committee. A-LV, SL, DH and KR contributed to trial co-ordination. HE, LH, A-LV, SL, KR, HH, and JD contributed to the project management. A-LV, SL, DH and KR contributed to data collection. LH, CP and DC contributed to data analysis. HE, LH, MW, CP, IG, JA, PH, CM, CH, DM, AW, DC and JD contributed to data interpretation. HE, LH, A-LV, SL, KM, LH-D, AH, M-LA-S, RS, DR, SR, PW, MH, CP, JM, IG, BM-A, EP, AC, JA, CC, PH, CM, CH, DM, AW, DC and JD contributed to writing the paper. HE, LH, and JD contributed to the creation of the table and figures.

Declaration of Interests

HE reports grants from NIHR HTA, during the conduct of the study, inside the submitted work. She reports grants from Roche and Sanofi-Aventis, personal fees and travel expenses from Daiichi-Sankyo and Astra Zeneca, travel expenses from Pfizer and Amgen and personal fees from Prime Oncology all outside the submitted work. KM reports an educational Grant for San Antonio BCS December 2017 from Roche. Advisory Board for Aphinity study 2017 from Roche. M-LA-S reports that since 16th April 2018, she has been a full-time employee of AstraZeneca with associated share options. DR reports personal fees and grants from Roche, during the conduct of the study; as well as personal fees from Novartis, Pfizer, Genomic Health, and Daiichi Sankyo, and grants from Celgene, all outside the submitted work. CP

reports personal fees and non-financial support from Roche Products Limited, personal fees and non-financial support from Amgen Limited, personal fees and non-financial support from Novartis UK Limited, personal fees and non-financial support from Pfizer UK Limited, outside the submitted work. IG reports employment from Novartis AG, outside the submitted work. CC reports grants from Genentech, Roche, Servier, grants from Astra-Zeneca, outside the submitted work, and is a member of AZ iMED External Science Panel.

PH reports grants from Roche, Pfizer, AstraZeneca, Novaratis, Eisai, and Daiichi-Sankyo, outside the submitted work. CM reports his institution received funding from NIHR for design and implementation of the economic evaluation of this trial. He was employed by the University of Leeds for the first four years of the trial's operation. The relationship was outside the submitted work. CH reports being a Member of the NIHR HTA Commissioning Board. DM reports personal fees from Roche/Genetech, outside the submitted work. AW reports personal fees from Roche, NAPP, Amgen, MSD, Novartis, Pfizer, AstraZeneca, Pierre Fabre, ACCORD, Athenex, Gerson Lehmann Group, Coleman Expert Network Group, Guidepoint global AW also reports personal fees and other from Lilly and Daiichi Sankyo; all outside the submitted work AW is leading the NCRI Breast Group Initiative to develop the next de-escalation trial for HER2 positive breast cancer. DC reports funds to his institution from Novartis, Astrazeneca, Pfizer, Roche, Eli-Lilly, PUMA, Daiichi Sankyo, Synthon, Seagen, Zymeworks, Elsevier, European Cancer Organisation, Celgene, Succint Medical Communications, Prima Biomed, Oncolytics Biotech (U.S) Inc, Celldex Therapeutics Inc, San Antonio Breast Cancer Consortium, Highfield Communication, Samsung Bioepis co Ltd, prIME Oncology, Merck Sharp Dohme Ltd, Prima BioMed Ltd, RTI Health Solutions, and Eisai, all outside the submitted work. LH, DH, KR and JD report grants from NIHR HTA Clinical

Trials grant (Persephone) during the conduct of the study. A-LV, SL, LH-D, AH, RS, SR, PW, MH, HH, MW, JM, B M-A, EP, AC, and JA have nothing to disclose.

Acknowledgements

The trial was funded by the National Institute of Health Research (NIHR) Health Technology Assessment Programme (HTA), funding project grant number 06/303/98. We acknowledge the 210 investigators and their teams from 152 participating UK centres who entered patients into the Persephone trial. Our gratitude also goes to the 4088 patients who kindly participated in our study. We wish to thank the independent members of the Trial Steering Committee, Tim Maughan (CRUK/MRC Oxford Institute for Radiation Oncology, Clinical Research Programmes, Department of Oncology, Oxford, UK.), Richard Gray (University of Oxford, Nuffield Department of Population Health, Medical Sciences Division, Oxford, UK) and Adele Francis (University of Birmingham) (deceased) for their expert guidance. We thank the Independent Data Safety and Monitoring Committee members: Richard Bell (Deakin University, Geelong, Australia), Roger A'Hern (Institute of Cancer Research – Clinical Trials Statistical Unit, Division of Clinical Studies, Royal Marsden NHS Foundation Trust, Sutton, Surrey, UK) and Marianne Nicolson (Anchor Unit, Aberdeen Royal infirmary, Aberdeen, UK), who have provided independent, expert professional advice throughout the study on patient safety, data and analysis. We thank the trials unit staff: Phase 3 coordination at Warwick Clinical Trials Unit, Coventry, UK; translational coordination at University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; and statistical analysis at Warwick Clinical Trials Unit, Coventry, UK. The trial conduct at UK sites would not have been possible without access to research nurses, data managers and other research staff funded via the NHS research and development departments (National Institute for Health Research

in England, Wales, and Northern Ireland; Scottish Cancer Research Network in Scotland). In addition we especially thank Catherine Durance personal assistant to HME, for her expert secretarial assistance in manuscript preparation and all documentation related to submission.

Table 1: Baseline characteristics, split by randomised group

Characteristic	12-month group (N=2045)	6-month group (N=2043)	Total (N=4088)
ER status *			
Negative	633 (31%)	632 (31%)	1265 (31%)
Positive	1412 (69%)	1411 (69%)	2823 (69%)
Chemotherapy type *			
Anthracycline based	854 (42%)	846 (41%)	1700 (42%)
Taxane based	200 (10%)	203 (10%)	403 (10%)
Anthracycline + Taxane based	989 (48%)	991 (49%)	1980 (48%)
No taxane and no anthracycline	2 (<1%)	3 (<1%)	5 (<1%)
Chemotherapy timing *			
Adjuvant	1737 (85%)	1731 (85%)	3468 (85%)
Neoadjuvant	308 (15%)	312 (15%)	620 (15%)
Trastuzumab timing *			
Concurrent	951 (47%)	952 (47%)	1903 (47%)
Sequential	1094 (53%)	1091 (53%)	2185 (53%)
Age at randomisation			
Median (range)	56 (23-82)	56 (23-83)	56 (23-83)
<35 years old	50 (2%)	45 (2%)	95 (2%)
35 – 49 years old	552 (27%)	557 (27%)	1109 (27%)

50 – 59 years old	608 (30%)	656 (32%)	1264 (31%)
60 +	835 (41%)	785 (39%)	1620 (40%)
Nodal Status at surgery [of the 3468 adjuvant patients]			
Negative	1003 (58%)	1019 (59%)	2022 (58%)
1–3 nodes positive	479 (28%)	486 (28%)	965 (28%)
4+ nodes positive	244 (14%)	211 (12%)	455 (13%)
Unknown	11 (<1%)	15 (<1%)	26 (<1%)
Tumour size ^ [of the 3468 adjuvant patients]			
<=2cm	824 (47%)	807 (47%)	1631 (47%)
>2 and <=5cm	778 (45%)	786 (45%)	1564 (45%)
>5cm	87 (5%)	83 (5%)	170 (5%)
Unknown	48 (3%)	55 (3%)	103 (3%)
Tumour Grade ^			
I (well diff.)	29 (1%)	34 (2%)	63 (2%)
II (mod. diff.)	628 (31%)	642 (31%)	1270 (31%)
III (poor diff.)	1322 (65%)	1297 (64%)	2619 (64%)
Unknown	66 (3%)	70 (3%)	136 (3%)
Ethnicity			
White	1658 (81%)	1648 (81%)	3306 (81%)
Asian	57 (3%)	52 (3%)	109 (3%)
Black	52 (3%)	45 (2%)	97 (2%)
Other	17 (<1%)	21 (1%)	38 (1%)
Unknown	261 (13%)	277 (13%)	538 (13%)

Menopausal status before chemotherapy			
Pre	567 (28%)	580 (29%)	1147 (28%)
Peri	110 (5%)	150 (7%)	260 (6%)
Post	1144 (56%)	1070 (52%)	2214 (54%)
Not assessable/Not available	224 (11%)	243 (12%)	467 (12%)
Reported prior use of cardiac medication			
Yes	44 (2%)	55 (3%)	99 (2%)
No	2001 (98%)	1988 (97%)	3989 (98%)
IHC[+]-score and FISH† positivity			
3+	1460 (71%)	1487 (73%)	2947 (72%)
2+ and FISH† positive	540 (27%)	497 (24%)	1037 (25%)
Not available	45 (2%)	59 (3%)	104 (3%)

* Stratification variable

^ of largest invasive tumour at diagnosis

[+] IHC = Immunohistochemistry

† FISH = Fluorescence in situ hybridization

6 men are included in the 4088 patients: 4 in the 12-month group and 2 in the 6-month group.

Table 2: Details of Events

Number of patients with a recorded …	12-month group (N=2045)	6-month group (N=2043)	Total (N=4088)
Death	156 (8%)	179 (9%)	335 (8%)
Breast cancer listed as a cause	129 (83%)	143 (80%)	272 (81%)
Breast cancer not listed as a cause, but a local or distant relapse reported	2 (1%)	6 (3%)	8 (2%)
Breast cancer not listed as a cause and no local or distant relapse reported	25 (16%)	30 (17%)	55 (17%)
Relapse *	218 (11%)	234 (11%)	452 (11%)
Local relapse	79 (4%)	77 (4%)	156 (4%)
Distant relapse	183 (9%)	190 (9%)	373 (9%)
Relapse or Death	247 (12%)	265 (13%)	512 (13%)

Second Primary	58 (3%)	52 (3%)	110 (3%)

* Patients can have both a local and distant relapse recorded

Table 3: Adverse Events and Cardiac Monitoring, over the two 6-month periods

Number of patients reporting at least one incidence of -	12-month group			6-month group		
	Overall	In months 1-6	In months 7-12	Overall	In months 1-6	In months 7-12
Adverse event with severe[&] CTCAE grade	459/1894 (24%)	350/1894 (18%)	259/1764 (15%)	373/1939 (19%)	370/1939 (19%)	8/93 (9%)
SAR to trastuzumab [$]	64/2044 (3%)	39/2044 (2%)	25/2019^ (1%)	29/2041 (1%)	28/2041 (1%)	2/2015^ (0·1%)
Clinical cardiac dysfunction [#]	224/1968 (11%)	164/1968 (8%)	157/1936 (8%)	155/1994 (8%)	126/1994 (6%)	96/1894 (5%)
Stopped trastuzumab permanently due to cardiac toxicity	146/1894 (8%)	63/1894 (3%)	83/1764 (5%)	61/1939 (3%)	60/1939 (3%)	1/93 (1%)
Cardiac death †	7/2044	0/2044	0/2019^	4/2041	0/2041	0/2015^
Cardiac death related to trastuzumab †	0/2044	0/2044	0/2019^	0/2041	0/2041	0/2015^
Low LVEF *	228/2040 (11%)	148/2040 (7%)	151/1938 (8%)	176/2038 (9%)	146/2038 (7%)	84/1749 (5%)

Significant falls in LVEF						
Absolute decrease of >=10% from baseline to <50%	163/1959 (8%)	98/1950 (5%)	102/1873 (5%)	132/1959 (7%)	102/1954 (5%)	60/1693 (4%)
LVEF<50% after a baseline of >=59%	108/1959 (6%)	63/1950 (3%)	71/1873 (4%)	86/1959 (4%)	70/1954 (4%)	32/1693 (2%)

[&] CTCAE grade >=3, or 2 for palpitations

[$] Denominators exclude the 3 patients known not to have received Trastuzumab

^ Denominators reduced due to either deaths or withdrawal of consent for follow-up within the 1st 6 months.[#] Clinical cardiac dysfunction = Symptoms of cardiac disease, and / or signs of congestive heart failure and / or new medication for cardiac disease

† 11 deaths were reported to have a 'cardiac' cause, either first cause or contributory. None occurred during the first 12 months after starting trastuzumab treatment. 9 patients died with no metastatic disease, and 2 had metastatic disease. In all cases trastuzumab was judged to be unrelated / unlikely to be related to cardiac problems

* Low LVEF = Number of patients with at least one LVEF<50%, or LVEF % unknown but classified on report as abnormal

Abbreviations:

SAR – Serious Adverse Reaction

LVEF = Left Ventricular Ejection Fraction

Figures in the Manuscript

Figure 1: Trial profile

Figure 2: Kaplan-Meier Plots of Disease-Free Survival (Panel A) and Overall Survival (Panel B), according to Randomised Group

Figure 3: Forest plots of Disease-Free Survival for all patients (Panel A) and adjuvant only patients (Panel B)

Figure 4: Kaplan-Meier Plots of Disease-Free Survival (Panel A) and Overall Survival (Panel B) from the landmark analysis from 6 months of Trastuzumab treatment, according to Randomised Group

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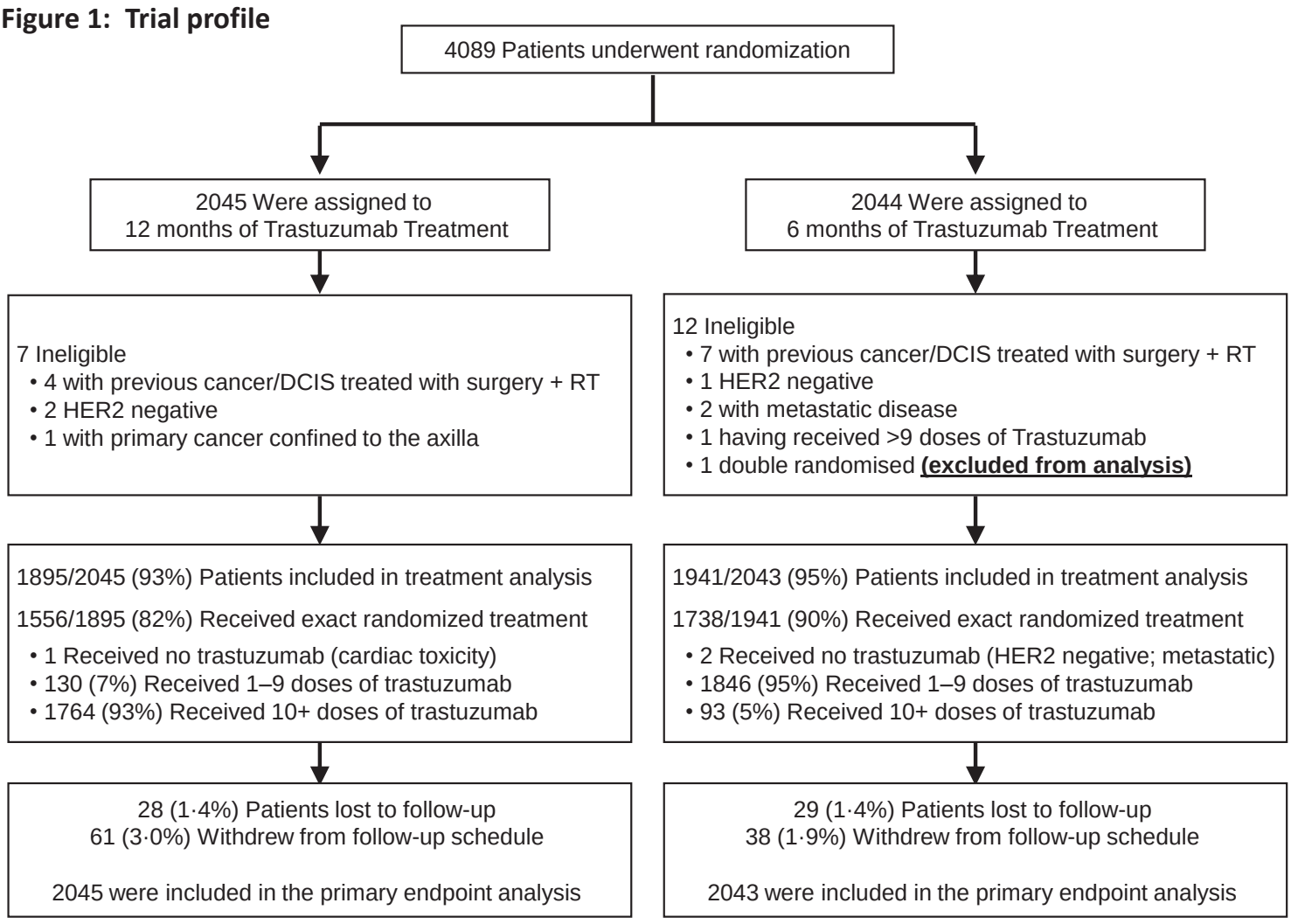
Figure 1



DCIS: ductal carcinoma in situ RT: radiotherapy

Figure 2

Figure 2 A: Kaplan-Meier Plots of Disease-Free Survival according to Randomised Group

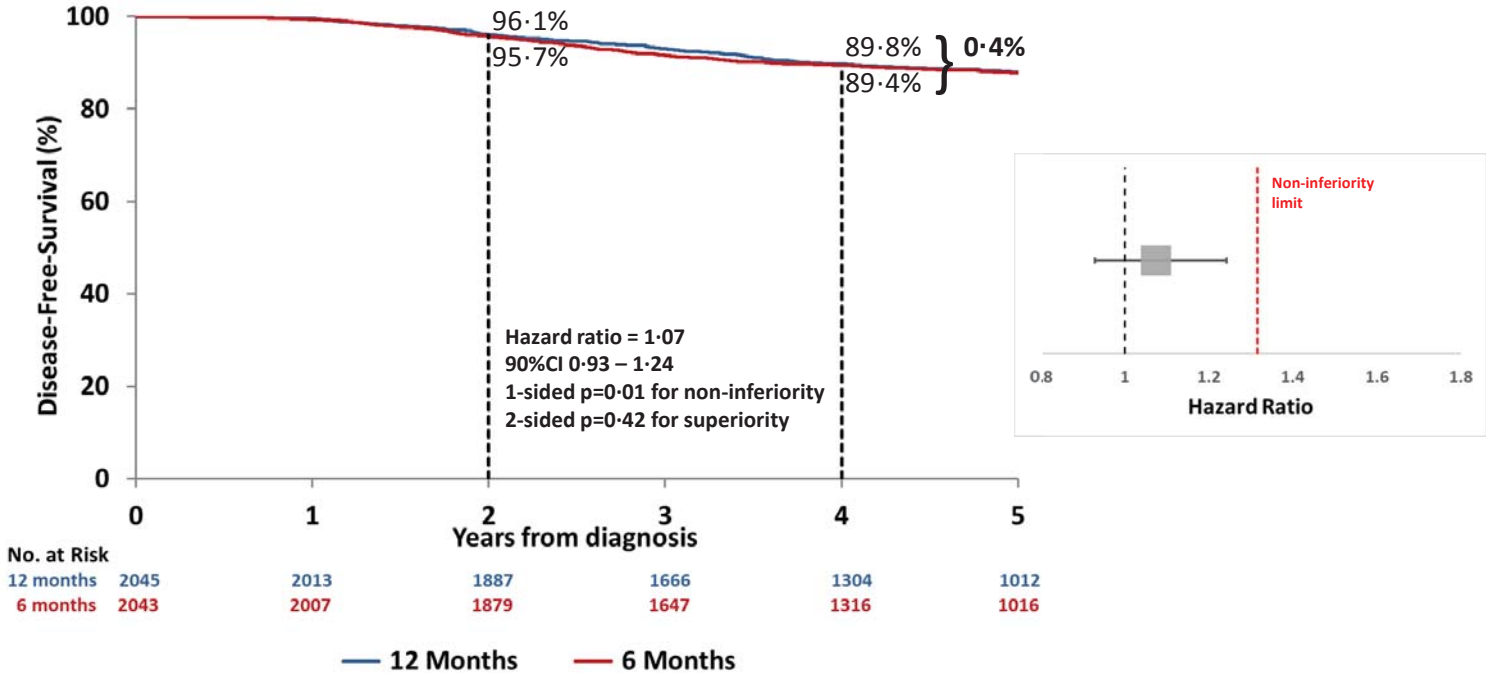
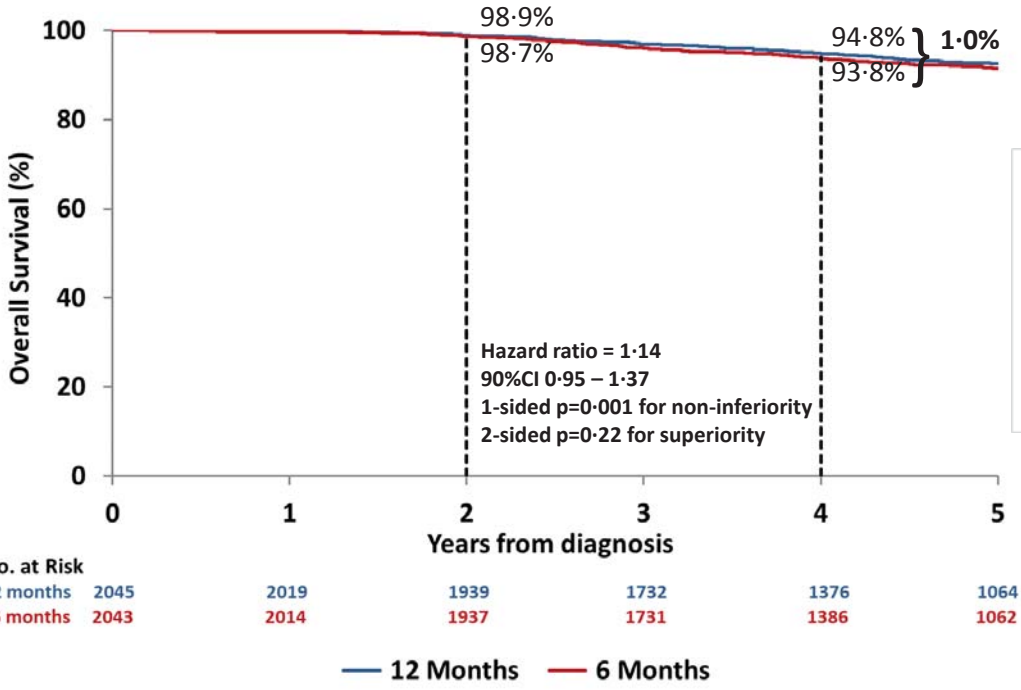


Figure 2 B: Kaplan-Meier Plots of Overall Survival according to Randomised Group



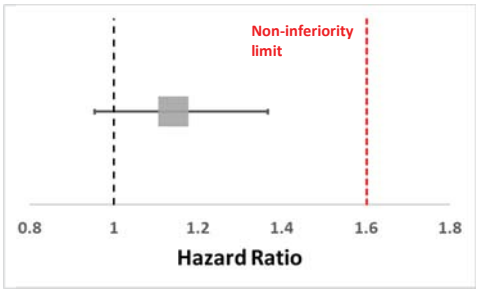


Figure 3

Figure 3 A: Forest plots of Disease-Free Survival for all patients

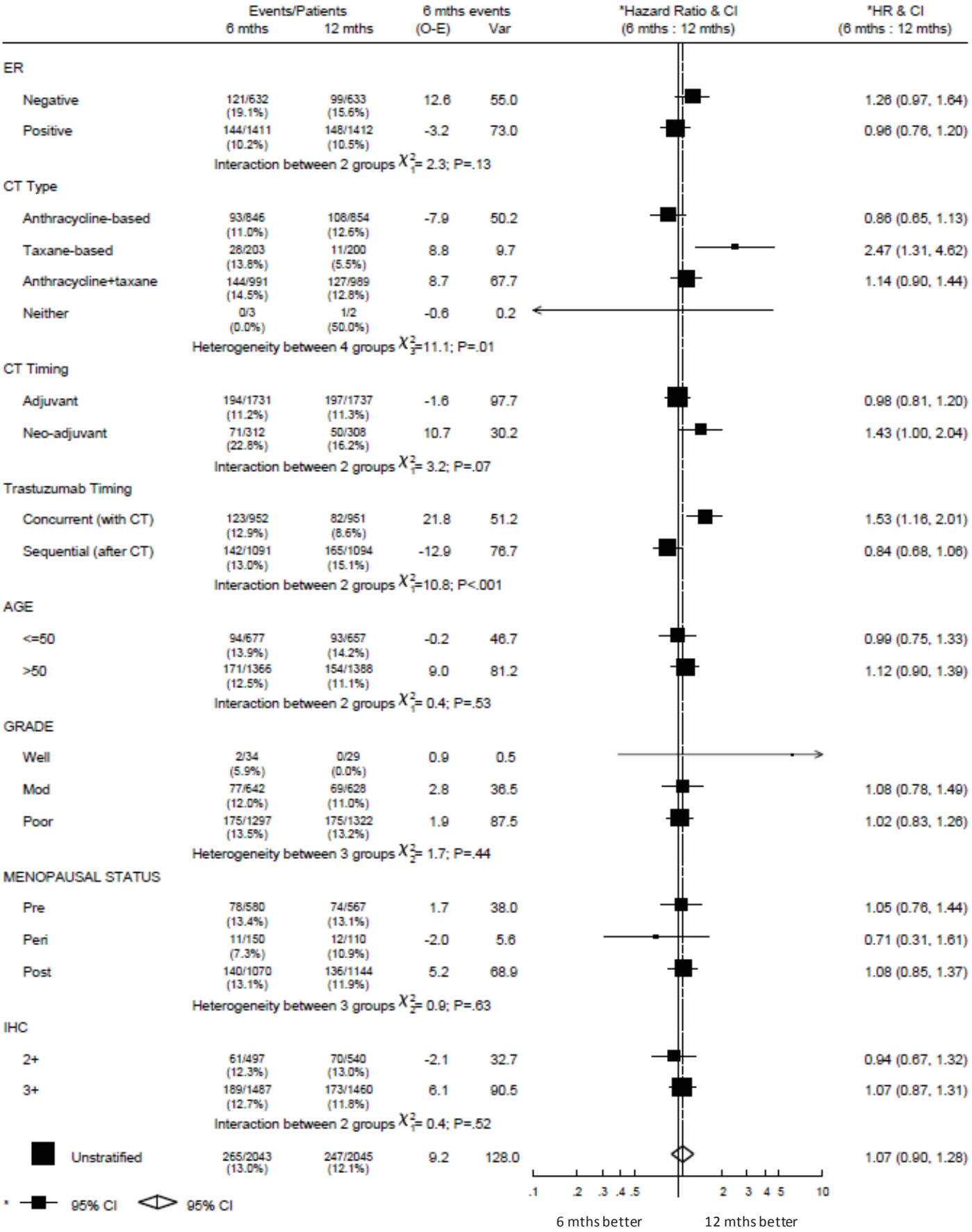


Figure 3 B: Forest plots of Disease-Free Survival for adjuvant only patients

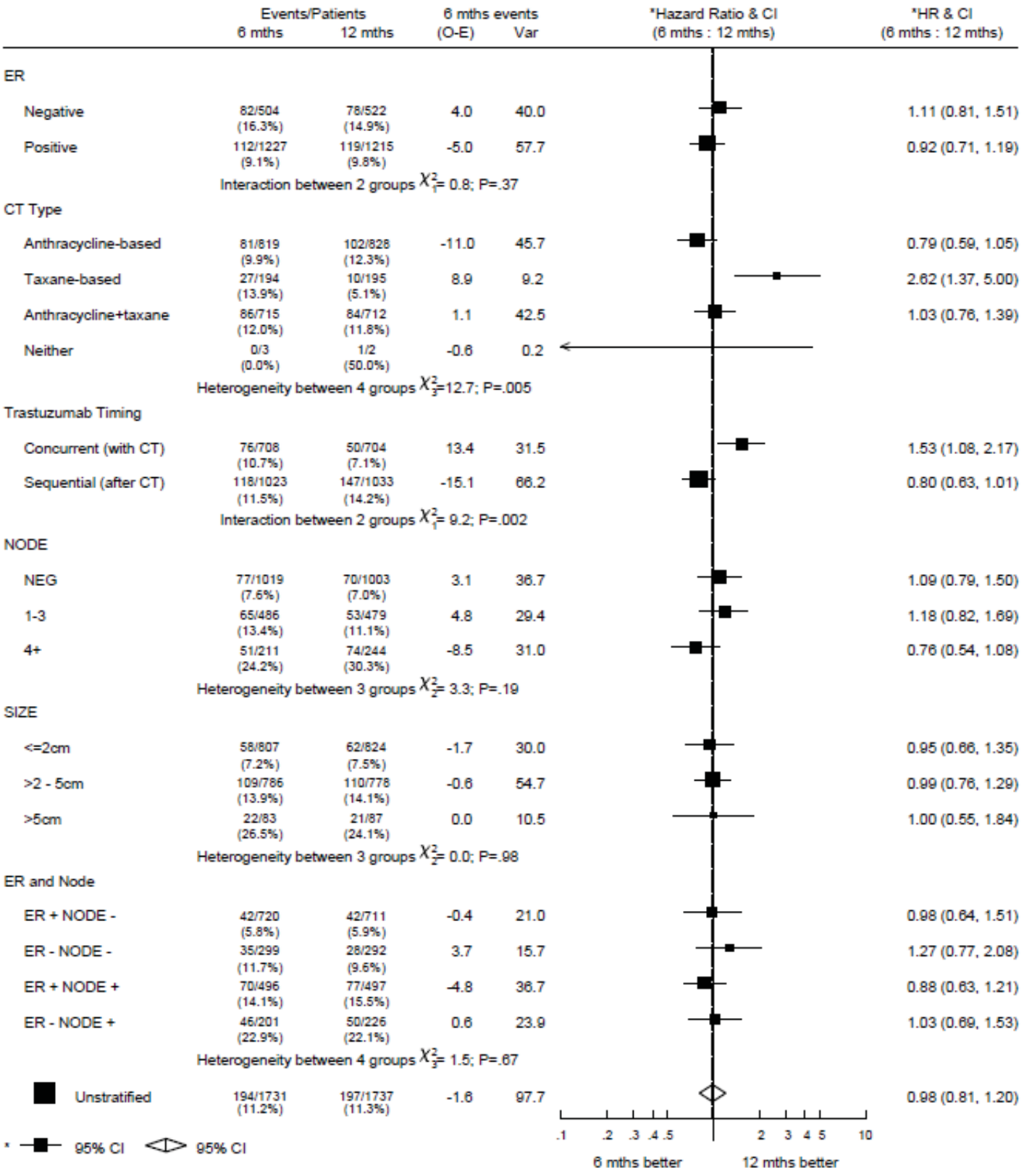


Figure 4

Figure 4 A: Kaplan-Meier Plots of Disease-Free Survival from the landmark analysis from 6 months of Trastuzumab treatment, according to Randomised Group

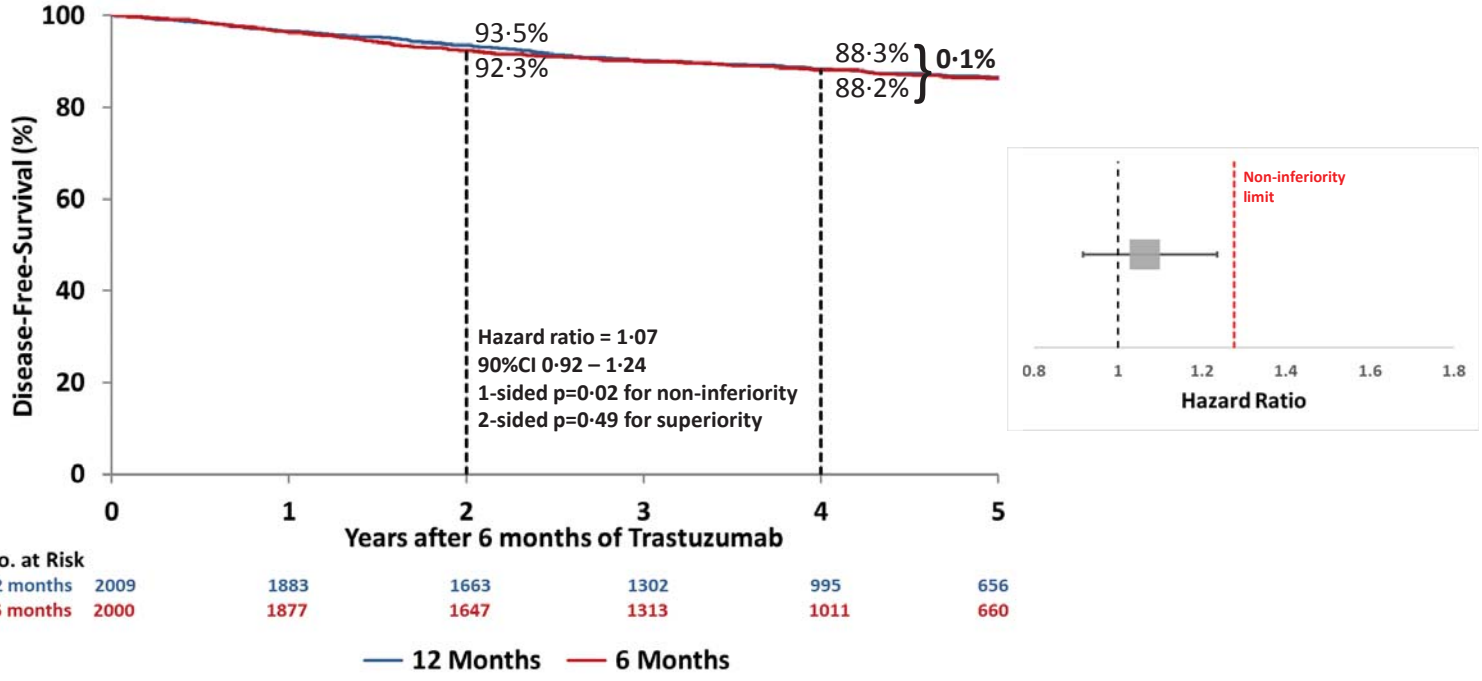


Figure 4 B: Kaplan-Meier Plots of Overall Survival from the landmark analysis from 6 months of Trastuzumab treatment, according to Randomised Group