NETSCC, HTA

22 October 2009

Persephone

Duration of Trastuzumab with Chemotherapy in Women with Early Breast Cancer: Six Months versus Twelve

Version 3.1, July 2009

EudraCT N°: 2006-007018-39
ISRCTN : 52968807
MREC: North West REC N°: 07/MRE08/35
NCRN No.: 4078

Signed by the Chief Investigator:
Dr Helena M. Earl

Date: 20/7/09

Cambridge Biomedical Research Centre

NHS National Institute for Health Research

Addenbrooke's Hospital NHS
Cambridge University Hospitals NHS Foundation Trust

UNIVERSITY OF CAMBRIDGE

HTA NHS Health Technology Assessment programme funded project www.hta.ac.uk

Warwick Medical School CLINICAL TRIALS UNIT

VERSION CONTROL

This document is only valid if the above signature is "wet" / original otherwise, it is considered as an uncontrolled copy of the protocol. Please check your site file to ensure you are using the correct / version.

List of abbreviations

ABPI	Association of the British Pharmaceutial Industry
AE	Adverse Event
ALT	ALanine Transaminase
ASCO	American Society of Clinical Oncology
AST	ASpartate Transaminase
BIG	Breast International Group
BNP	Brain Natriuretic Peptide
CHF	Congestive Heart Failure
CI	Chief Investigator
CI	Confidence Interval
CMF	Cyclophosphomide Methotrexate 5-Fluorouracil
CRF	Case Report Form
CT	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTCR-BR03	Cambridge Translational Cancer Research - Breast Study numero 3
CXR	Chest X-Ray
DFS	Disease Free Survival
DNA	DeoxyriboNucleic Acid
DSMC	Data and Safety Monitoring Committee
ECD	Epirubicin Cyclophosphamide Docetaxel
ECG	Electrocardiogram
ECHO	Echocardiography
ECMF	Epirubicin Cyclophosphomide Methotrexate 5-Fluorouracil
ECOG	Eastern Co-operative Oncology Group
ECP	Epirubicin Cyclophosphamide Paclitaxel
ER	Oestrogen receptor
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
FEC	5-Fluorouracil Epirubicin Cyclophosphamide
FISH	Fluorescent In Situ Hybridisation
GCP	Good Clinical Practice
Hb	Hemoglobin
HER2	Human Epidermal growth factor Receptor 2
HR	Hazard Ratio
HTA	NHS Heath Technology Assessment Programme
IHC	Immuno-Histo-Chemistry
INCa	Institut National du Cancer
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LVEF	Left Ventricular Ejection Fraction
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Multi-Centre Ethics Committee
MUGA	MUltiple Gated Acquisition scan
NCCHTA	National Co-ordinating Centre for the Heath Technology Assessments
NCI	National Cancer Institute (USA)
NCRI	National Cancer Research Institute.
NEJM	New England Journal of Medicine
NSABP	National Surgical Adjuvant Breast and Bowel Project
NYHA	New-York Heart Association
OS	Overall Survival
P	probability
PI	Principal Investigator
PO	by mouth
PSSRU	Personal Social Services Research Unit (PSSRU)
q	every
QALYs	Quality adjusted life years
QoL	Quality of Life
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SNP	Single Nucleotide Polymorphism
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAC	Docetaxel Doxorubicin Cyclophosphamide
TBA	To Be Appointed
TMG	Trial Management Group
ULN	Upper Limit of Normal
WBC	White blood cell count
WHO	World Health Organisation

Table of contents

1. Trial Summary

***PERSEPHONE* - Primary objective:** A phase III, randomised trial comparing 6 months trastuzumab treatment with 12 months, in women with HER2 positive early breast cancer, in terms of efficacy (disease-free and overall survival), cost-effectiveness (Health Resource Use and Quality of Life) and safety (cardiac and other toxicity).

***PERSEPHONE* - Secondary objectives - Sub-studies:**

1. ***Trans - PERSEPHONE:*** Tumour blocks (paraffin-embedded) will be collected prospectively from patients in the study, for molecular and candidate gene analysis as prognostic and predictive markers (separate protocol).
2. ***Trans - PERSEPHONE - SNPs:*** Blood samples will be collected prospectively from patients in the study, for Single Nucleotide Polymorphism analysis to research genetic / pharmaco-genetic determinants of prognosis and treatment response (separate protocol).

Lead Investigators:	Helena Earl (CI), David Miles, David Cameron, Andrew Wardley.
Clinical co-ordinators:	Rajiv Agrawal, Rozenn Allerton, Peter Bliss, Jeremy Braybrooke, Carlos Caldas, Stephen Chan, Michael Crawford, Sue Dean, Lydia Fresco, Christopher Gallagher, Rosalind Glasspool, Robert Grieve, Adrian Harnett, Tamas Hickish, Steve Houston, Luke Hughes-Davies, Clive Irwin, Alison Jones, Robert Leonard, Michael Lind, Andreas Makris, Karen McAdam, Janine Mansi, Susan O'Reilly, Ann Robinson, Timothy Perren, Pippa Riddle, Diana Ritchie, Peter Simmonds, Mark Verrill, Charles Wilson
Clinical surgical co-ordinators:	Gordon Wishart, Anthony Skene.
Cardiology Advisor:	David Dutka
Protocol authors:	Helena Earl, Anne-Laure Vallier, Janet Dunn, Louise Hiller, Chris McCabe.
Statisticians:	Janet Dunn, Louise Hiller
Trial co-ordinators:	Shrushma Loi and Jasvinder Sandhu (Warwick), Anne-Laure Vallier (Cambridge) and Linda Jones (Translational research nurse co-ordinator)
Pharmacovigilance:	Cambridge Clinical Trials Centre (Helena Earl [CI] and Anne-Laure Vallier)
Pharmacist Advisor:	Anita Chhabra (Cambridge)
Pathologist Advisor:	Elena Provenzano (Cambridge)
Health Economics Advisor:	Christopher McCabe and Clare Hulme, Academic Unit of Health Economics, Institute of Health Sciences, University of Leeds
Phase III co-ordinating centre:	Warwick Medical School Clinical Trials Unit, University of Warwick
Translational co-ordinating centre:	Experimental Cancer Medicine Centre (NCRI and CR UK), University of Cambridge and Cambridge University Hospitals NHS Foundation Trust
Translational Sub-committee:	Carlos Caldas (Chairman), Elena Provenzano, Helena Earl, Anne-Laure Vallier, Linda Jones, Jean Abraham and Mahesh Iddawela.
Number of patients to be enrolled:	4,000
Indication:	Early breast cancer patients, HER2 positive, eligible for adjuvant or neo-adjuvant chemotherapy.
Trial Sponsors:	Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge
PHARE Group France:	Xavier Pivot (CI), Iris Pauporte (Management and Regulatory Affairs), Sylvie Detry (Co-ordination and Pharmacovigilance) and Xavier Paoletti (see Appendix 7).

Persephone

Rationale

The incidence of breast cancer continues to rise in the Western Europe and US and breast cancer remains a major health problem despite considerable improvements in treatment of the disease both in the adjuvant and in the metastatic setting. Trastuzumab (Herceptin®) treatment in women with early breast cancer and HER2 positive disease, has proved a major advance and has demonstrated incontrovertibly the value of targeted therapy in the adjuvant setting for breast cancer in particular and cancer in general. However, the use of 12 months trastuzumab in the majority of studies is not based on evidence. It is reasonable to consider that since the beneficial effect of adjuvant trastuzumab is detected early in follow-up (median 1 year), that the majority of the adjuvant benefit results from the first 6 months of therapy. This hypothesis is supported by evidence from the FinHer study which, with only 9 weeks trastuzumab demonstrates a similar-sized benefit to 12 months treatment, when given concurrently with chemotherapy. The ***Persephone*** trial will compare 6 months treatment with 12 months, in terms of safety and efficacy.

Primary endpoint

- Disease-free survival non-inferiority (equivalence) of 6 months trastuzumab compared with 12 months in women with early breast cancer.

Secondary endpoints (clinical)

- Overall survival non-inferiority (equivalence) of 6 months trastuzumab to 12 months in women with early breast cancer.
- Expected incremental cost effectiveness (Cost per Quality Adjusted Life Year Gained) for 6 months trastuzumab versus 12 months trastuzumab.
- Cardiology - function as assessed by left ventricular ejection fraction (LVEF) 3 monthly during trastuzumab therapy, and analysis of predictive factors for development of cardiac damage.

Study design

- A phase III, prospective, randomised trial of trastuzumab duration (6 months versus 12 months) in the adjuvant and neo-adjuvant setting for patients with early stage HER2 positive breast cancer.
- Detailed data on resource use and quality of life will be collected in an early cohort of ***Persephone*** patients (300-500 patients) for Health Economic Analysis. Quality of life data will be collected on all patients (EuroQoL).
- Assessment of cardiac function will be made with reference to methods used for assessment and age and other co-morbidities as risk factors. Cardiac function will be routinely assessed prior to commencement of trastuzumab and 3 monthly whilst on treatment.

Sample size determination

The power calculations assume that the disease-free survival (DFS) of the standard treatment of 12 months trastuzumab will be 80% at 4 years. On this basis, with 5% 1-sided significance and 85% power, a trial randomising 4000 patients in total (2000 in each arm) will have the ability to prove non-inferiority of the experimental arm, defining non-inferiority as ‘no worse than 3%’ below the control arm 4 year DFS.

Analysis

- Primary endpoint of disease-free survival will be assessed using Kaplan-Meier survival curves and treatment tested using Cox Proportional Hazards analysis, with and without adjustment for the stratification and baseline prognostic factors, on an intention-to-treat basis.
- Secondary outcomes of overall survival will be assessed using Kaplan-Meier survival curves and treatment tested using Cox Proportional Hazards analysis, with and without adjustment for the stratification and baseline prognostic factors, on an intention-to-treat basis.
- The analyses of all other secondary endpoints will be undertaken using the appropriate statistical analysis tools.

Duration of treatment

- The trial employs either 6 or 12 months trastuzumab in women with early stage breast cancer. All patients will receive chemotherapy either in the adjuvant or neo-adjuvant setting. Trastuzumab will be given either concurrently or sequentially with respect to chemotherapy, and so the total duration of treatment (chemotherapy and trastuzumab) will vary depending on the precise combination employed.

Key inclusion criteria

- Women with histologically confirmed invasive breast cancer.
- HER2 positive breast cancer (3+, or 2+ and FISH amplified).
- Patient of sufficient risk to require chemotherapy (anthracycline-based [no taxane], or taxane-based [with anthracyclines], or taxane-based [no anthracyclines] combinations).
- Adjuvant or neo-adjuvant chemotherapy.

Key exclusion criteria

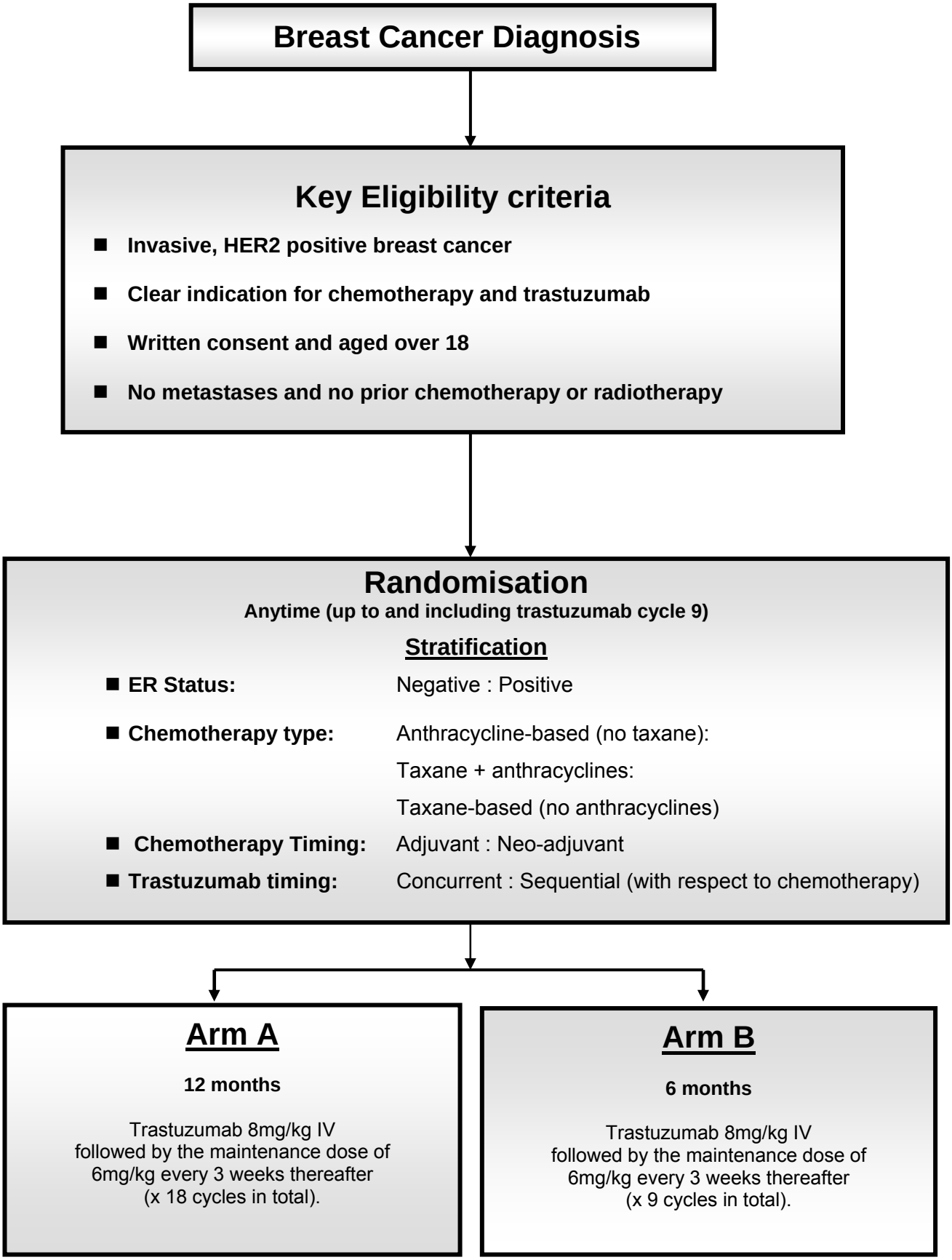
- Not suitable for chemotherapy in the opinion of the responsible clinician.
- Evidence of metastatic disease.

PERSEPHONE – Sub-studies:

- ***Trans - PERSEPHONE:*** Tumour blocks (paraffin-embedded) will be collected to discover molecular predictors of survival with respect to duration of trastuzumab treatment. Analysis of tumour tissue will involve (i) tissue microarrays for immunohistochemistry (IHC) of protein gene products and in situ hybridisation analysis, and (ii) whole-genome profiling using expression and DNA microarrays.

- ***Trans - PERSEPHONE – SNPs:*** Blood samples will be used to discover single nucleotide polymorphisms (SNPs) as genetic / pharmacogenetic determinants of prognosis, toxicity and treatment outcome.

2. Trial Schema



Persephone

3. Introduction

Trastuzumab (Herceptin®) has been tested extensively in the adjuvant setting in women with HER2 positive early breast cancer, and shown to provide significant benefits in terms of disease-free and overall survival compared to adjuvant chemotherapy alone. The results of three large randomised trials were presented in a special session at the American Society of Clinical Oncology 2005 (ASCO), and detailed interim analyses of the trials were published in the New England Journal of Medicine (NEJM) in October 2005(1,2). The clinical improvement for trastuzumab is the largest benefit ever seen in breast cancer trials, and is remarkable both for its magnitude, and also the demonstration of benefit so early in follow-up.

The HERceptin Adjuvant (HERA) trial was an international, multi-centre, randomised trial, which compared one or two years trastuzumab given every 3 weeks, with observation in patients with HER2-positive and either node-negative or node-positive breast cancer, who had completed loco-regional therapy and at least 4 cycles of neoadjuvant or adjuvant chemotherapy. 1694 patients were assigned 2 years trastuzumab, 1694 one year, and 1693 were in the observation arm with chemotherapy alone. Results were reported in the NEJM paper for the one year trastuzumab compared with chemotherapy alone (1). At the first planned interim analysis (median follow-up 1 year), 347 events (recurrence of breast cancer, contra-lateral breast cancer, second non-breast malignant disease, or death) were observed: 127 events in the trastuzumab group and 220 in the observation group. The unadjusted hazard ratio (HR) for an event in the trastuzumab group compared with the observation group was 0.54 (95% Confidence Interval, 0.43-0.67; P<0.0001 by the log rank test crossing the interim analysis boundary), representing an absolute benefit in terms of disease-free survival (DFS) at 2 years of 8.4. percentage points. Severe cardiac toxicity developed in 0.5 percent of the women treated with trastuzumab. The 2-year follow-up analysis of the HERA trial has now been published in the Lancet and demonstrates a benefit for overall survival (OS) as well as DFS (HR for OS = 0.66 [95% CI 0.47-0.91]; p=0.0115: updated HR for DFS = 0.64 [95% CI 0.54-0.76]; p<0.0001) (3). These results show that trastuzumab after adjuvant chemotherapy has a significant benefit after a median follow-up of 2 years. The emergence of this benefit after only 2 years reinforces the importance of trastuzumab in the treatment of women with HER2-positive early breast cancer.

The second paper published in the NEJM (2) included the combined results of two US trials, which compared adjuvant chemotherapy with or without concurrent trastuzumab in women with surgically removed HER2-positive breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial NSABP-B-31 compared doxorubicin and cyclophosphamide followed by paclitaxel every 3 weeks (group 1) with the same regimen plus 12 months of trastuzumab beginning with the first dose of paclitaxel (group 2). The North Central Cancer Treatment Group trial N9831 compared three regimens: doxorubicin and cyclophosphamide followed by weekly paclitaxel (group A), the same regimen followed by 52 weeks of trastuzumab after paclitaxel (group B), and the same regimen plus 52 weeks of trastuzumab initiated concomitantly with paclitaxel (group C). The studies were amended to include a joint analysis comparing groups 1 and A (the control group) with groups 2 and C (the trastuzumab group). Group B was excluded because trastuzumab was not given concurrently with paclitaxel. By March 15, 2005, 394 events (recurrence, second primary cancer, or death before recurrence) had been reported, triggering the first scheduled interim analysis. Of these, 133 were in the trastuzumab group and 261 in the control group (hazard ratio, 0.48; P<0.0001). This result crossed the early stopping boundary. The absolute difference in disease-free survival between the trastuzumab group and the control group was 12 percent at three years. Trastuzumab therapy was associated with a 33 percent reduction in the risk of death (P=0.015). The three-year cumulative incidence of class III or IV congestive heart failure or death from cardiac causes in the trastuzumab group was 4.1 percent in trial B-31 and 2.9 percent in trial N9831. Trastuzumab combined with paclitaxel after doxorubicin and cyclophosphamide improves outcomes among women with surgically removed HER2-positive breast cancer.

The BCIRG study of trastuzumab in women with early breast cancer (BCIRG 006) examined concurrent treatment of trastuzumab with a non-anthracycline-containing chemotherapy regimen (docetaxel and either carboplatin or cisplatin). Interim results were reported by Slamon at the 2005/06 San Antonio Breast Cancer Conferences (4,5). BCIRG 006 was a large, randomized phase III trial of adjuvant doxorubicin, cyclophosphamide followed by docetaxel with or without trastuzumab versus trastuzumab, docetaxel and either carboplatin or cisplatin (TC[H]) in women with HER2-expressing node positive or high risk node-negative operable breast cancer. This study showed significant improvement in DFS for the use of Herceptin®. At San Antonio 2005 a subgroup analysis demonstrated an interesting interaction between HER2 over-expression and co-expression of topoisomerase II alpha, and the benefit of anthracycline treatment (6,7). Patients with combined over-expression were disadvantaged on the TCH arm, presumed due to the lack of an anthracycline, despite the addition of trastuzumab. However, the updated results presented at San Antonio in 2006 did not confirm topoisomerase II alpha overexpression as a predictive marker for anthracycline benefit. This study now simply confirms the effect of the

addition of trastuzumab to chemotherapy in women with early HER2 positive breast cancer. The putative effect of co-overexpression of topo-II alpha requires further investigation with regard to interaction with anthracyclines.

Beneficial results for trastuzumab given for just 9 weeks, concurrently with docetaxel or vinorelbine were reported from the FinHer study at the San Antonio Breast Cancer Conference 2005, and in the NEJM in February 2006 (8). This study compared docetaxel with vinorelbine for the adjuvant treatment of patients with early breast cancer. Women with tumors that over-expressed HER2 were also assigned to receive chemotherapy with or without concomitant trastuzumab. A total of 1010 women were recruited with axillary-node-positive or high-risk node-negative cancer to receive three cycles of docetaxel or vinorelbine, followed by (in both groups) three cycles of fluorouracil, epirubicin, and cyclophosphamide. The 232 women whose tumors had an amplified HER2 gene were further assigned to receive or not to receive nine weekly trastuzumab infusions, concurrently with the docetaxel or vinorelbine. The primary end point was recurrence-free survival. Recurrence-free survival at three years was better with docetaxel than with vinorelbine [91 percent vs. 86 percent; hazard ratio for recurrence or death, 0.58; 95 percent confidence interval, 0.40 to 0.85; P=0.005), but overall survival did not differ between the groups (P=0.15)]. Within the subgroup of patients who had HER2-positive cancer, those who received trastuzumab had better three-year recurrence-free survival than those who did not receive the antibody (89 percent vs. 78 percent; hazard ratio for recurrence or death, 0.42; 95 percent confidence interval, 0.21 to 0.83; P=0.01). Docetaxel was associated with more adverse effects than was vinorelbine. Importantly despite trastuzumab being given immediately before anthracyclines, this arm was <u>not</u> associated with decreased left ventricular ejection fraction or cardiac failure. Adjuvant treatment with docetaxel, as compared with vinorelbine, improves recurrence-free survival in women with early breast cancer. A short course of trastuzumab administered concomitantly with docetaxel or vinorelbine is effective in women with breast cancer who have an amplified HER2 gene.

The above studies clearly demonstrate the effectiveness of adjuvant trastuzumab in patients with HER2 positive breast cancer, however important questions about adjuvant trastuzumab in women with early breast cancer still remain, in particular the duration of therapy question (9). All studies reported have used 12 months trastuzumab apart from the FinHer study, which used just 9 weeks of therapy, immediately post-operatively with either docetaxel or vinorelbine. The choice of 12 months trastuzumab in the large studies is not evidence-based, and it would be reasonable to hypothesise that since the effect of adjuvant trastuzumab is detected so early in follow-up (median follow-up 1 year), that the majority of the adjuvant effect is being seen in the first 6 months of therapy. Based on these Finnish results, the French Group (Institut National du Cancer [INCa]) has developed the PHARE clinical trial to compare 6 versus 12 months trastuzumab. In an International Collaboration with the PHARE group, ***Persephone*** will carry out a pre-planned joint analysis of results, which will allow an equivalence or non-inferiority comparison between 6 and 12 months duration of trastuzumab at the 2% level (absolute). The International Collaboration requires at least 7,000 patients to be entered, but the statisticians on the project are encouraging randomisation of as many patients as possible to improve the 'certainty' of the outcome of the trial. In a recent article in Cancer World (10) the French group detailed that to be significant an International collaboration requires recruitment of over 4000 patients in the UK.

Persephone will allow recruitment of HER2-positive patients who require chemotherapy. Patients can have either adjuvant or neo-adjuvant chemotherapy, anthracycline or taxane-based chemotherapy, and trastuzumab either concurrently or sequentially with chemotherapy. Patients will be randomized before the start of trastuzumab treatment, and health resource use and quality of life data will be collected on all patients during trastuzumab therapy.

Trastuzumab is the first targeted biological therapy to have reported demonstrable benefit in the adjuvant setting in cancer, but there are many similar compounds in the pipelines of all global pharmaceutical companies. It is very important that an international collaboration tackles the question of duration of such therapy. The question of the potential equivalence of 6 months and 12 months therapy, whilst of enormous importance to the wider cancer community, would not be in the immediate interests of the commercial sector to answer. The success of this study will be dependent on non-commercial, academic, and national groups collaborating in an effort to maximize recruitment. The ***Persephone*** group is clear that it will also be important to answer the more generic question about newer targeted therapies:

'Is 6 months of targeted biological therapy for early cancer, sufficient?'

4. Objectives of the study

Primary endpoint

- Disease-free survival non-inferiority (equivalence) of 6 months compared with 12 months trastuzumab in women with early breast cancer.

Secondary endpoints (clinical)

- Overall survival non-inferiority (equivalence) of 6 months compared with 12 months trastuzumab in women with early breast cancer.
- Expected incremental cost effectiveness (Cost per Quality Adjusted Life Year Gained) for 6 months versus 12 months trastuzumab.
- Cardiology function as assessed by left ventricular ejection fraction (LVEF) 3 monthly during trastuzumab therapy, and analysis of predictive factors for development of cardiac damage.

5. Persephone: trial design

This is a phase III clinical trial randomising 4000 patients in total to receive either 6 months of trastuzumab (experimental arm) or 12 months of trastuzumab (standard arm).

5.1 First 100 concomitant chemotherapy and trastuzumab patients 'pilot' study

Since the second part of the various chemotherapy schedules (taxanes or CMF) can be given concomitantly with trastuzumab, the first 100 patients on ***Persephone*** receiving concomitant chemotherapy and trastuzumab will provide data 'in real time' on serious adverse effects and treatment delay, for this category of patient. These data will be collected and analysed by the ***Persephone*** trial office and discussed by the Trial Management Group.

5.2 Eligibility criteria

Inclusion criteria

- Histological diagnosis of invasive breast cancer.
- No evidence of metastatic disease.
- Known hormone receptor status.
- Overexpression of HER2 receptor.
- Clear indication for neo-adjuvant or adjuvant chemotherapy based on clinical and histopathological features.
- Patient fit to receive neo-adjuvant or adjuvant chemotherapy and trastuzumab in the opinion of the responsible physician.
- No previous diagnosis of malignancy unless:
  - managed by surgical treatment only, and disease-free for 10 years.
  - previous basal cell carcinoma, cervical carcinoma *in situ* or ductal carcinoma *in situ* of the breast.
- Non-pregnant and non-lactating, with no intention of pregnancy during chemotherapy, and agrees to adopt adequate contraceptive measures if pre-menopausal and sexually active.
- No concomitant medical or psychiatric problems that might prevent completion of treatment or follow-up.
- Women or men 18 years or older.
- Written informed consent for the study given at any time before the 10th cycle of trastuzumab.
- Patient must have adequate bone marrow, hepatic, and renal function.*

**** Recommendations:***

- *Hb > 10 g/dL; WBC > 3 $\times$ 10^9/L; platelets > 100 x 10^9/L*
- *Bilirubin within normal range*
- *AST/ALT $\leq$ 2 x ULN*
- *Alkaline phosphatase $\leq$ 2 ULN*
- *Creatinine $\leq$ 1.5 x ULN*
- *No active, uncontrolled infection*

Exclusion criteria

- Clinically significant cardiac disease including :
    - History of documented Congestive Heart Failure
    - High-risk uncontrolled arrhythmias
    - Angina pectoris requiring medication
    - Clinically significant valvular disease
    - Evidence of transmural infarction on ECG
    - Poorly controlled hypertension
- History of myocardial infarct during the 6 months prior to recruitment.
- Any significant co-morbidity in the opinion of the responsible physician adding to the risks associated with cytotoxic chemotherapy for instance: severe chronic obstructive pulmonary disease, poorly controlled diabetes.
- History of allergy to drugs containing polysorbate 20 and the excipient TWEEN 80® and history of allergy to mouse proteins.
- Inability to comply with protocol requirements.
- Patient having received more than 9 cycles of trastuzumab.
- Any other condition, which in the local investigator's opinion would make the patient unsuitable for participating in the trial.

5.3 Schedule of assessments and procedures (see Appendix 1)

Pre-randomisation screening investigations

- **Pathology investigations**
  ER status must be defined at randomisation.
  Definitive HER2 status must be available at randomisation.

  Definition of HER2 positive overexpression
  Hospitals which are entering patients into the trial must ensure that laboratories are complying with the UK Guidelines for HER2 testing (11).

- **Staging investigations other than cardiac**
  Required staging investigations will be minimal in keeping with standard UK practice in breast cancer management. All examinations will need to be completed in compliance with local IR(ME)R Employer's Procedures at each site. An ARSAC certificate is not required if the investigations (CXR, CT scan or isotope bone scan) are carried out according to standard practice at the centre.

  All patients should have a full blood count (FBC), biochemical screen, to include liver and bone function tests.
  In the case of abnormal full blood count or abnormal liver or bone biochemistry*, further staging investigations are advised, in accordance with standard practice at the centre.

  ***Recommendations** — *Hb ≤10 g/dL; WBC ≤ 3 × 10^9/L; platelets ≤ 150 x 10^9/L*
  AST/ALT ≥ 2 x ULN, Alkaline phosphatase ≥ 2 ULN

- **Cardiac investigations**

* It is recommended that patients should not have clinically significant cardiac abnormalities and should not have had a myocardial infarction during the 6 months prior to recruitment. Cardiac function should be assessed by physical examination and echocardiography [ECHO], or multi-gated acquisition cardiac scanning [MUGA*]). LVEF must be within the normal limits of the institution. A decision to administer or 'hold' a dose of trastuzumab on account of a fall in LVEF must be made based on the recommendations in Table 1 section 6.3.

LVEF must be carried out after 6 months of Herceptin (9 cycles), and after 9 months (13-14 cycles) in both arms of the study. The protocol requests LVEF in addition at 12 months (after completion of Herceptin) where possible in both arms of the study.

It is anticipated that the most frequent randomisation point will be after 9 cycles of Herceptin. Patients being randomised at this point should have LVEF carried out after randomisation to avoid selection bias.

* An ARSAC certificate is not required if the MUGA are carried out according to standard practice at the centre.

6. *Persephone* treatment plan

6.1 Trial treatment

Initial / Loading dose

The starting / loading dose of trastuzumab is 8mg/kg.
The maintenance dose (6mg/kg) is given 3 weeks after the starting / loading dose, and subsequent doses are given 3 weekly at 6mg/kg. However, it is acceptable that weekly maintenance doses can be given but this must be discussed with the study co-ordinating centre prior to the patient starting Herceptin.

Research arm: Patients will receive 9 cycles of trastuzumab (6 months arm).

***Standard arm*:** Patients will receive 18 cycles of trastuzumab (12 month arm).

Trastuzumab delays

- Patients are not allowed to 'hold' treatment on account of cardiac toxicity on more than two occasionsfor more than a total of 3 months. ThisIt is because it is likely that minimum length of a 'hold' because of cardiac dysfunction will be 6 weeks and therefore a maximum of two "holds" will be allowed for cardiac toxicity.
- PIs in centres using chemotherapy protocols with up-front taxanes and concomitant trastuzumab, will likely discontinue trastuzumab during subsequent anthracyclines. Timing of restarting trastuzumab in these circumstances will be at the discretion of the treating clinician and may be more than 3 months.
- Patients who have a 'hold' of trastuzumab for whatever reason, should receive a total of either 9 or 18 cycles depending on randomisation.

Dose banding

Dose banding is acceptable and should be decided according to local policy.

Rates of Infusion

Cycle 1: It is recommended that trastuzumab should be administered intravenously over a 90-minute period. Patient must remain under observation for 6 hours from the start of the trastuzumab infusion.

Cycle 2- onwards:
If no adverse events occured with the first infusion, subsequent infusions should be given according to local practice. In cases where patients have reacted to previous cycles, the period of observation should remain 6 hours.

Trastuzumab ± chemotherapy in *Persephone* delivered at home

Trastuzumab can be administered at home if this is part of standard practice at the site, and following contractual agreement between the Health Care Provider and the individual site to deliver trastuzumab ± chemotherapy within ***Persephone***.

Concurrent trastuzumab and chemotherapy.

It is advised that patients receiving combination treatment should as standard, either (i) have the initial dose of trastuzumab on the day before administration of chemotherapy. Subsequent doses of chemotherapy may be given on the same day immediately after trastuzumab if the initial dose is well tolerated. Or (ii) have the initial dose of trastuzumab 2 weeks after starting docetaxel, paclitaxel or other concurrent chemotherapy. However it is the responsibility of the principal investigator at the treating site, to adhere to local guidelines for delivery of trastuzumab.

6.2 Timing of Chemotherapy

Patients can receive trastuzumab sequential to or concurrent with adjuvant or neo-adjuvant chemotherapy.
Patients must be randomised preferably before cycle 9 and certainly prior to cycle 10 of trastuzumab.

Adjuvant chemotherapy

Sequential treatment
Trastuzumab can be administered sequentially following **all types of adjuvant breast cancer chemotherapy**.

Concurrent treatment
Trastuzumab can be administered concurrently with some chemotherapy regimens but not others. For a comprehensive list of the chemotherapy regimens, see Appendix 5. In cases where trastuzumab can be administered concurrently, the treatment can be started with any cycle of chemotherapy as indicated.

Neo-adjuvant chemotherapy

Sequential treatment
Trastuzumab can start before or after surgery. If starting just before surgery, trastuzumab treatment can continue every three weeks without interruption even during the peri-operative period.

Concurrent treatment
Trastuzumab is administered concurrently with some chemotherapy regimens and not others. For a comprehensive list of standard chemotherapy regimens, see Appendix 5. The decision to give trastuzumab concurrently with chemotherapy is made by the responsible treating clinician and is in accordance to local standard protocols. In cases where trastuzumab is to be administered concurrently, the treatment can be started with any cycle of chemotherapy as indicated. Trastuzumab treatment can also continue every three weeks without interruption during the peri-operative period, at the discretion of the local clinician.

6.3 Standard chemotherapy treatments

All patients randomised will receive or be scheduled to receive standard chemotherapy regimens as per local institutional protocols. These protocols will depend on the prognosis of the patient and during the 'lifetime' of the trial, depending on licensing and NICE guidance.

Chemotherapy within trials is accepted for the Neo-tAnGo trial (epirubicin / cyclophosphamide, paclitaxel ± gemcitabine), TACT2 trial (epirubicin [standard or accelerated], then CMF or capecitabine), which are adjuvant chemotherapy trials open at the time of writing of the ***Persephone*** protocol. In general most trials will be compatible with ***Persephone***, and will be considered by the trial management group as and when they are activated. Trastuzumab is licensed for use in patients receiving chemotherapy for early breast cancer, and for both sequential (after chemotherapy) and concurrent use (with chemotherapy).

Chemotherapy will be administered following the normal practice of the centre with respect to all co-medication and procedures for the safe administration of cytotoxic chemotherapy.

Reverse-sequence taxane-first chemotherapy

There is now some evidence that taxane-first sequencing may produce higher response rates in neo-adjuvant therapy (28). Reversed sequence treatment to allow immediate concomitant taxane and trastuzumab will be permitted in the trial.

All chemotherapy regimens which include anthracyclines, and/or taxanes are acceptable on the *Persephone* trial.

See Appendix 5 for commonly used UK chemotherapy regimens. This list is NOT exhaustive, and chemotherapy not included is still acceptable for ***Persephone***.

6.4 Management in response to cardiac toxicity

Delayed scheduled doses

If the administration of trastuzumab is more than 28 days since the previous dose, it is recommended to re-start the treatment as soon as possible with a loading dose of 8mg/kg followed by the usual maintenance dose of 6mg/kg every 3 weeks thereafter.

Patients are not allowed to 'hold' treatment on account of cardiac toxicity for more than a total of 3 months. It is likely that minimum length of a 'hold' because of cardiac dysfunction will be 6 weeks and therefore a maximum of two"holds" will be allowed for cardiac toxicity.

Trastuzumab related toxicity

Infusion-Associated Symptoms

Patients with pulmonary disease or pre-existing respiratory compromise may be at increased risk from serious infusion-associated symptoms and need to be monitored with extreme caution.

During the first infusion with trastuzumab, a symptom complex commonly consisting of chills and/or fever is observed in about 40% of patients. The symptoms are usually mild to moderate in severity. They rarely cause trastuzumab discontinuation. Other signs and/or symptoms may include nausea, vomiting, pain, rigors, haedache, dizziness, dyspnoea, hypotension, rash and asthenia. The symptoms occur infrequently with subsequent trastuzumab infusions. Very rarely patients experienced a severe/life threatening-infusion-related event.

If infusion symptoms develop, stop the infusion until resolved. Supportive treatment : oxygen, beta agonists, antihistamines or corticosteroids for example can be administered. Restart the infusion at a slower rate when symptoms have resolved. If hypersensitivity occurs again, STOP INFUSION.

Patients who experience mild, moderate or severe infusion reactions on the first dose can be retreated with trastuzumab. Premedication with corticosteroids, antihistamines, and antipyretics before subsequent trastuzumab infusion are recommeneded.

There are no data regarding the most appropriate method of identification of patients who may be retreated with trastuzumab after experiencing a severe hypersensitivity reaction. Trastuzumab has been readministered to some patients who fully recovered from a previous severe reaction. Prior to readministration of trastuzumab, the majority of these patients were prophylactically treated with pre-medications including antihistamines and corticosteroids. While some of these patients tolerated retreatment, others had severe reactions again despite the use of prophylatic pre-medication.

Cardiac symptoms

All patients must have a baseline LVEF measurement by the method which is normal for the institution (ECHO, or MUGA). LVEF will be monitored every three months (every 4 cycles) according to the schedule of assessments. If an adverse event is related to cardiac dysfunction, an additional measurement should be performed.

In case of LVEF decrease, a patient may continue or discontinue trastuzumab as outlined in Table 1. In case of New York Heart Association class III/IV cardiac function (Appendix 4), trastuzumab has to be discontinued even after resolution of symptoms or normalisation of LVEF. However, patients will remain in the study and complete all assessments as planned.

Dyspnoea, oedema and reduced cardiac LVEF has been observed with trastuzumab. They are generally more common when trastuzumab is given concomitantly with the chemotherapy. Treatment commonly included diuretics, cardiac glycosides, and/or angiotensin-converting enzyme inhibitors.

Haematological

An increased incidence of anaemia, leukopenia and thrombocytopenia was observed in the treatment group receiving trastuzumab and chemotherapy. Haematological toxicity is infrequent following the administration of trastuzumab given as single agent.

Concurrent Chemotherapy-related Toxicity
Chemotherapy toxicity should be recorded according to the Common Toxicity Criteria for Adverse Events (Appendix 6) for each cycle of chemotherapy with trastuzumab.

Toxicity will be managed at the discretion of the doctor as per standard practice.

Haematological and non-haematological toxicity

Table 1: Recommendation to follow for trastuzumab related toxicity

Toxicity related to trastuzumab	Recommendation
a- Haematological toxicity	
Haematological	Continue trastuzumab
b- Non-haematological toxicity	
Non-haematological o grade 1 or 2	Continue trastuzumab
Non-haematological o grade 3 or 4, o and toxicity resolved within a maximum of 5 weeks calculated from last planned administration	'Hold' trastuzumab until recovery to grade ≤2
Non haematological o grade 3 or 4, o and toxicity NOT resolved to grade ≤2	Discuss with the trial co-ordination centre
Non haematological o grade 3 or 4 o upon re-challenge with trastuzumab	Discontinue trastuzumab therapy permanently
c- Cardiac toxicity	
Asymptomatic patients	
o Absolute reduction of less than 10% from baseline o and LVEF within normal limits	Continue
o Absolute reduction of less than 10% o and LVEF 1-5% below normal limits	Continue
o Absolute reduction of less than 10% o and LVEF ≥6% below normal limits	Continue*
o Absolute reduction of 10-15% o and LVEF within normal limits	Continue
o Absolute reduction of 10-15% o and LVEF below normal limits 1% or more	Hold*
o Absolute reduction of ≥16%	Hold*
Symptomatic cardiac dysfunction	Discontinue and refer to a cardiologist

*repeat LVEF assessment before 6 weeks. If criteria for continuation are met resume trastuzumab. The maximum permitted dose-delay for a single 'hold' due to reduction of LVEF is 3 months for recovery. Patients are not allowed to "hold" treatment on more than two occasions and / or more than 3 months.

6.6 Disease progression

If at any stage during the treatment there is suspicion of relapse or disease progression, this should be confirmed radiologically if assessed clinically. The clinical trials office must then been notified of any relapse or progression, and further treatment remains at the discretion of the clinician.

6.7 Patient withdrawal

Patients should discontinue trial medication in the following circumstances:

- The patient opts to withdraw from the study or chooses not to comply with study procedures.
- The patient is inadvertently enrolled without meeting the eligibility criteria (except in extenuating circumstances in which case continuation must be agreed with the trials office).
- The investigator decides that the patient should be withdrawn from the study due to toxicity.
- The patient has not recovered from toxicity to an extent that allows further trastuzumab treatment.
- The patient becomes pregnant or fails to use adequate birth control (for those patients who are able to conceive).
- Confirmed disease progression (according to WHO criteria).

Withdrawal of patients for any reason should be communicated to the ***Persephone*** trial office as soon as possible by telephone. Reasons for withdrawal should be recorded on the Treatment Summary Form.

Follow-up data will be collected on all withdrawn patients (this also applies to patients who opt to withdraw consent for the trial unless they explicitly forbid further data to be collected).

6.8 Endocrine therapy

Concurrent hormone therapies are not recommended with chemotherapy, but can be used concurrently with trastuzumab. Hormonal treatment received by the patient must be recorded on the Annual Follow-up form.

Following completion of chemotherapy and definitive surgery, systemic hormonal therapy is advised for women with ER-positive disease. All endocrine therapy is at the discretion of the responsible clinician in accordance with standard local therapy protocols; the following are guidelines only. For women who remain pre-menopausal after completion of chemotherapy, hormonal therapy options include ovarian suppression and tamoxifen. Entry into the Breast International Group (BIG) EORTC trial SOFT or TEXT should be considered. For postmenopausal women, tamoxifen or aromatase inhibitors can be used for a minimum of 5 years (or tamoxifen for 2-3 years switching to an aromatase inhibitor 2-3 years [19]).

6.9 Radiotherapy

Radiotherapy will be given after definitive surgery according to local protocols.

Radiotherapy can be given concomitantly with trastuzumab. If radiotherapy treatment is given this must be recorded on the Radiotherapy form.

7. Tissue and blood collection

7.1 Tumour blocks collection (Trans - Persephone)

- ***Trans - PERSEPHONE:*** Tumour blocks (paraffin-embedded) will be collected to discover molecular predictors of survival with respect to duration of trastuzumab treatment. Analysis of tumour tissue will involve (i) tissue microarrays for immunohistochemistry (IHC) of protein gene products and in situ hybridisation analysis, and (ii) whole-genome profiling using expression and DNA microarrays.

Centres are strongly encouraged to provide tissue for the ***Trans - Persephone*** sub-study, after obtaining informed consent from patients (see patient information sheet and consent form). The collection will be done by contacting the pathologists directly.

1) Adjuvant setting

Following randomisation, pathologists will be asked to provide a representative sample of the tumour as follows :

- a representative paraffin-embedded tumour block of the tumour
- a paraffin-embedded tumour block containing normal tissue (same quadrant as the tumour).

2) Neo-adjuvant setting

Following surgery, pathologists will be asked to provide:

- a representative diagnostic tumour block (core biopsy)
- a representative paraffin-embedded block of the tumour (from operation post chemotherapy)
- a paraffin embedded-tumour block containing normal tissue (same quadrant as the tumour).

A small amount of representative tissue will be removed from the blocks and processed by the Cambridge Translational Cancer Research Laboratories. Blocks will be then sent back to the pathology department.

7.2 Blood collection for Pharmacogenetics/Genetics Study (Trans - Persephone-SNPs)

Patients consenting to take part in the **Trans - Persephone-SNPs** sub-study will be asked to give a blood sample (2x9 ml EDTA) at one occasion.

Blood could be taken at anytime before, during or after chemotherapy. If blood samples are taken during the chemotherapy phase, they should preferably be taken on the day that patients are due to receive a cycle of chemotherapy, in order to provide adequate cell counts to provide enough DNA to assay.

Samples will be used to assay for pharmacogenetics studies and prognostic and predictive candidate germline mutations.

8. Study organisation

8.1 Randomisation of patients

Randomisation can take place at anytime before the cycle 10 of trastuzumab treatment.

A sufficient amount of time needs to be taken into consideration to organise the exams pre-treatment.

An eligibility form should be completed prior to randomisation. Details should then be phoned or faxed through to Warwick Clinical Trials Unit, **between 9 am and 5 pm, Monday to Friday**.

☎: 0247 6150 402 🖷: 0247 6150 549

The name of the investigator directly responsible for the patient's care will be requested at randomisation. Investigators must be pre-registered with the trials unit before they are permitted to enrol patients on the study.

8.2 Data collection

Case record forms will be designed by Cambridge Clinical Trials Centre in collaboration with the Warwick Medical School Clinical Trials Unit and will comprise the following:

Table 2: **Standard forms and summary of data collected**

Form	Brief summary of data recorded	Schedule of submission
1.Eligibility Form	Confirmation of full inclusion criteria and satisfactory staging investigations	Fax immediately with Patient Randomisation Form
2.Randomisation Form	Details of stratification variables; optional consent issues; patient randomisation number and treatment allocated. Patient height and weight	Fax immediately with Patient Eligibility Form
3.Diagnosis biopsy form for Neo-adjuvant patients	Diagnostic biopsy histology; details of planned surgery	Within 1 month of randomisation
4.Surgery Form	Full details of tumour excision and histology	Within 1 month of randomisation
5.Trastuzumab Treatment Form	Trastuzumab therapy and cardiology assessments details per 3 month period (+/- 4 cycles).	Within 1 month of completion of 4 cycles of trastuzumab
6.Treatment Summary Form	Date, dose and drugs given for each cycle of chemotherapy. Number of trastuzumab cycles received. Additional cardiology assessments.	Within 1 month of all treatment and assessment completion
8. Radiotherapy Form	Area treated and number of doses given	Within 1 month of radiotherapy
9. Principal Investigator declaration Form	Confirmation that the data have been collected according regulation and protocol.	Within 1 month after all treatment completion
10. Annual Follow-Up Forms	Endocrine treatment details, late toxicities, relapse, date and cause of death if applicable	Within 2 months of form being sent to Site (form will be sent on each anniversary of randomisation)

Ad hoc **forms**

- Serious Adverse Event form (refer to section 9.2).
- Relapse/Death Report form (refer to section 10.2).
- Hospital Transfer form

Data collection will be the responsibility of Warwick Medical School Clinical Trials Unit and Cambridge Clinical Trials Centre. Sample collection, anonymisation, and good laboratory practice will be the responsibility of Cambridge Clinical Trials Centre and Cambridge Translational Cancer Research Laboratories. All data will be handled and stored in accordance with the 1998 Data Protection Act.

8.3 Data quality assurance & monitoring

Case report forms must be submitted to the ***Persephone*** office in a timely manner according to the schedule outlined in Table 2. On receipt, all forms will be checked for completeness and congruity. Forms containing empty data fields or data anomalies will be queried and returned to site for resolution.

8.4 Conduct of study

Persephone will be conducted in accordance with UK legislation and ICP Good Clinical Practice (GCP) Guidelines. See section 17.

All participating clinical investigators will be required to sign an investigator agreement and supply the study office with a current curriculum vitae.

All site personnel involved in the conduct of the trial will be asked to attend a start-up meeting which will cover trial rationale, protocol procedures, and collection and reporting of data. These meetings will be conducted by the ***Persephone*** study office personnel either in person or by telephone if appropriate. Following this, all sites will be provided with a site file containing instructional materials and documentation required for the conduct of the study. The ***Persephone*** study office will offer continued support for sites via telephone, fax, email, and mail.

End of the trial
The end of the trial will be last patient's last visit or after the biological material has been processed whichever come later.

Archiving period
The archiving period will begin immediately after this end of the trial. All essential trial documents (including patient notes) must be retained for at least 5 years following the end of the trial. The trial sponsor will notify the centres when documents may be destroyed.

8.5 Trial Management Group

This group will be responsible for the day-to-day running of the study. This consists of the Chief Investigator (Helena Earl) and other applicants on the HTA grant award (Janet Dunn) together with project manager (Senior) Warwick, Co-ordinator (Cambridge), Louise Hiller (trial statistician, Warwick), monitor (Warwick), programmer (Warwick), data manager (Warwick), and administrators (Cambridge and Warwick).

8.6 Trial Steering Committee

All members are identified in the trial summary. The trial steering committee will meet annually to formally discuss the conduct of the study and to receive reports, and agree all publications. The chief investigator will discuss all matters of importance with regard to the conduct and running of the study, as and when this may prove necessary.

8.7 Data and Safety Monitoring Committees (DSMCs)

Persephone DSMC

An independent data and safety monitoring committee has been established for this study and their main objective is to advise the trial steering committee as to whether there is evidence or reason why the study should be amended or terminated based on recruitment rates or safety and efficacy. Reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes (not formally tested outside of the trial statistical analysis plan, to be agreed with the DSMC) will be presented to a Data and Safety Monitoring Committee for their review alongside results from other relevant trials. Recommendations from the DSMC will be summarised and circulated to the Trial Steering Committee and proposed international DSMC via the trial management group.

International DSMC

It is the intention to establish an international data and safety monitoring committee whose role will be to monitor worldwide evidence and on-going Herceptin® duration trials, including Persephone and PHARE (appendix 7). It is proposed that members of the Persephone DSMC may also serve on the international DSMC but the roles and responsibilities will be clearly defined for each committee.

8.8 Monitoring by the NCCHTA

The National Co-ordinating Centre for the Health Technology Assessments [NCCHTA] (the funders of the PERSEPHONE Study), will appoint an **Independent Trial Steering Committee**, which will consist of an independent chairman, and 3 other independent members. Members of the operational trial management group, will also sit on this committee. The study conduct and progress will be monitored by the NCCHTA and both the NCCHTA and the Independent Trial Steering Committee, will receive 6 monthly reports on the study, and following completion a full report in the form of a monograph for publication by the HTA. The senior project manager (Warwick) has the responsibility of managing the processes necessary for the timely conduct and reporting of the study, including managing the HTA grant, and preparing the final report.
The NCCHTA must be informed of any intended publications or presentations at national or international conference (oral or poster) 28 days or more before presentation or publication.

9. Safety reporting

The collection and reporting of data on adverse events and serious adverse events will be in accordance with EU Directive 2001/20/EC and UK legislation. This pharmacovigilance will be managed by the Cambridge Clinical Trials Centre, which includes the assessment and reporting of all serious adverse events (SAEs) in the trial, together with the assessment and reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs).

9.1 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

The incidence and nature of AEs is an important endpoint for this study and all AEs should be documented on the Adverse Event/Toxicity forms completed for each cycle of chemotherapy and trastuzumab. However, the following should NOT be reported as an AE:

- A pre-existing condition, unless the condition worsens or episodes increase in frequency during the reporting period and the investigator deems this related to use of the study drug
- Symptoms relating to disease progression or death unless the investigator deems them related to use of the study drug
- Symptoms related to treatment for disease progression

9.2 Serious Adverse Events (SAEs)

Definitions

A SAE is any untoward medical occurrence that at any dose results in:

- death
- initial or prolonged inpatient hospitalisation (excluding hospitalisation for study drug administration) *****
- a life-threatening experience (i.e. immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly or birth defect

***** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure, for continued observation. Hospitalisation for a pre-existing condition, including elective procedures, which has not worsened, does not constitute a serious adverse event.

Reporting SAEs

Please complete and fax all SAEs Forms to the Cambridge Clinical Trials Centre on 🖷: +44 (0)122 3348 071

For SAE related queries please telephone either:

Cambridge Persephone Trial Office on ☎: + 44 (0)122 3348 086 OR

Warwick Persephone Trial Office on ☎: +44 (0)247 6150 492

Monday to Friday between 9am and 5pm

If required, investigators should also report SAEs to their Trust Research & Development department in accordance with the local institutional policy.

Documenting SAEs

The responsible clinician must determine the severity of an event (according to the NCI CTCAE), and relatedness and expectedness of the events to the study drugs. Seriousness, relatedness, and expectedness will also be independently assessed by the Chief Investigator (or Deputy). A serious adverse event judged by the Investigator or Chief Investigator to have a reasonable causal relationship with the trial medication will be regarded as a serious adverse reaction (SAR). If the event meets the definition of a serious adverse reaction that is unexpected in nature it will be classified as a suspected unexpected serious adverse reaction (SUSAR).

Reporting period for SAEs

If a patient experiences a SAE after the informed consent document is signed, but before receiving her first dose of study drug within the trial, the event will be reported only if the investigator believes that the event may have been caused by a protocol procedure.

Details of all SAEs will be documented from the point of randomisation within the trial until 30 days post-treatment (i.e. 30 days from last administration of the study drug).

SAEs occurring after a patient's 30-day follow-up assessment should be reported only if the investigator believes that the study drug or a protocol procedure may have caused the event.

Follow-up of SAEs

In the case of a SAE, the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Follow-up may continue after completion of protocol treatment if necessary. Follow-up information will be noted on the Serious Adverse Event Form by ticking the box marked 'follow-up' and sending to the ***Persephone*** Translational study office as information becomes available. Extra annotated information and/or copies of test results should also be provided where available.

Reporting of SARs to regulatory authorities

The ***Persephone*** Office at the Cambridge Clinical Trials Centre will report all fatal or life threatening SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Multi-Centre Ethics Committee (MREC) within 7 days of receiving initial notification from the study site. Any follow-up information will be provided within an additional 8 days. Non-fatal and non-life threatening SUSARs will be reported within 15 days. The Cambridge Clinical Trials Centre will also submit an annual safety report to the MHRA and MREC summarising all SARs .

The Cambridge Clinical Trials Centre will forward details of SUSARs to all Investigators in the form of a safety report produced every 6 months.

10 Patient follow-up

10.1 Follow-up schedule

Patients will be followed-up routinely every 3 months for the first year following start of trastuzumab treatment, then 6-monthly for the subsequent year, and then yearly. Follow-up data will be requested annually based on the randomisation date anniversary.

10.2 Relapse and death

Long-term follow-up will include dates and sites of first relapse (see table 5), both local and systemic treatment at relapse, and date and cause of death. This is necessary for the study's endpoints of disease-free and overall survival. As soon as definite confirmation has been obtained, a Relapse/Death form should be completed and returned to the trials unit. Patients who relapse should remain on follow-up.

***Table 3*: Definition of relapse and death**

Loco-regional	Ipsilateral breast/ chest wall, axillary and ipsilateral supraclavicular nodal relapse
Distant	Distant relapse (excluding ipsilateral supraclavicular nodes)
2nd primary	Including contralateral malignant breast disease
Death	Death from any cause

11. Quality of life study

Quality of life sub-study will be carried out using the EQ-5D. Patients will be provided with baseline questionnaire by study site personnel. Quality of life data will be collected at different time points as follows (see Appendix 1):

- Prior to randomisation (baseline questionnaire)
- 3-monthly for a year following the start of the trastuzumab (both arms of the trial) (3 monthly questionnaire)
- then every 6 months up to year 2 (6 monthly questionnaire).

12. Health economics study

Economic evaluation of Persephone
The objective of the economic evaluation is to identify the within trial and long term incremental cost effectiveness ratio for trastuzumab compared to standard care of surgery/radiotherapy/chemotherapy in the treatment of women with early breast cancer.

Within trial cost effectiveness analysis

Measurement of outcomes: The primary outcome measure of the trial is disease free survival. The trial economic evaluation will, for consistency, use the same primary outcome measure. However, as economic evaluations are designed to inform resource allocation decisions, evaluations will also be produced using overall survival and Quality adjusted life years (QALYs) outcome measures. These measures are more useful for comparing the value of trastuzumab with all uses of limited health care resources [20]. Data on disease free survival and overall survival will be collected as part of the Case Report Form (CRF).
The estimation of QALYs requires the production of utility weights for each health state observed in the trial population. We will use the EQ-5D (EuroQol) instrument for this purpose. [21,22]. The EQ-5D is a very simple instrument to complete and will therefore be collected at baseline and at 3 monthly intervals until the end of follow-up. This will limit the need to interpolate quality of life between observation points and the associated inaccuracy in the estimation of the HrQol differences between therapies [23].

Measurement of resource use: NHS resource use associated with each treatment modality will be collected either through the CRF (investigations, drugs, referrals for other services) or through a patient diary (contact with primary, community and social care services).

The patient diary will be used to collect data on out-of-pocket expenses associated with their condition (travel expenses, over-the-counter medicines and supplements, 'complementary' therapies not funded by NHS, home-help). The data for collecting the indirect costs associated with each intervention (time away from work for patient and/or carer) will be collected through the patient diary.

The patient diary will be designed to allow tick-box completion where ever possible. Whilst patients are attending at monthly or more frequent intervals they will receive and return their patient diary at the outpatient clinic. For patients attending less frequently than monthly, they will receive the patient diary by post and will return it to the study centre using a free post envelope. These patients will receive a written reminder to return their diary if it has not been received two weeks after the end of the cover it period. The completeness of the patient diary returns will be monitored and for patients experiencing difficulties providing data the feasibility of collecting the data via a telephone interview will be explored.

Identifying unit costs: Unit costs for health service resources will be obtained from national sources such as the PSSRU, the BNF and NHS Reference cost database. Where national unit costs are not available the finance departments of trusts participating in the study will be asked to provide local cost data. The mean of these costs will be used as the unit cost estimate in the analysis.

Perspective for analysis: The primary cost effectiveness analyses will adopt the perspective of the NHS and social services. Secondary analyses will adopt a societal perspective taking account of productivity costs and out-of-pocket expenditures incurred by the patients. There is currently substantial uncertainty about the best method for estimating productivity costs. If this uncertainty has been resolved at the time of the analysis we will adopt the recommended method, if not we will undertake sensitivity analysis to demonstrate the impact of using friction cost based estimate rather than human capital based estimates of productivity costs.

Discounting: There remains some uncertainty regarding the correct approach to discounting costs and benefits. The analysis will follow the recommendations current at the time. Under current recommendations this would mean that costs and outcomes would be discounted at 3.5% per annum [24-26].

Analysis of uncertainty: The non-parametric bootstrap method will be used to produce a within-trial probabilistic sensitivity analysis of the incremental cost effectiveness ratio. In addition to presenting the expected incremental cost effectiveness ratio, we will present the scatterplot on the cost effectiveness plane, the 95% cost effectiveness ellipse and the cost effectiveness acceptability curve [20].

Sub-group analyses: Where analyses of the clinical outcome data suggest a substantial difference in absolute benefit from treatment in *a priori* identifiable groups, cost effectiveness analyses will be presented for these sub-groups. The definition of substantial will inevitably involve some subjective judgement which will be made in discussion with clinicians, not relying solely on evidence for statistical significance, but also taking account of *inter alia*, the biological plausibility of a differential absolute effect.

Modelling the long term cost effectiveness of trastuzumab

A long term cost effectiveness analysis is required to capture the full impact of any therapy where it is possible that there is a difference in mortality between the interventions.

The exact structure of the cost effectiveness model will be established in discussions with the clinicians on the study team and after analysis of the adverse event data observed in the trial. It is likely that the model will be a markov or semi-markov state model. As far as possible the transition rates for the model will be estimated from the clinical trial data. Model parameters for which data could not be collected within the trial; e.g. long term outcomes following cardiovascular adverse events, we will follow recommended best practice in identifying and synthesising the best available evidence in the literature [26,27].

The long term cost effectiveness modelling will adopt the strategies for addressing issues of perspective and discounting as the within trial analysis.

Details of trastuzumab treatment related toxicity will be collected with each cycle of treatment using the NCI CTCAE scoring system. Data will also be collected on hospital admissions, extra outpatient visits, use of anti-emetics, antibiotics, vascular treatment, and other supportive drugs to contribute to a health economics analysis of additional health costs related to the treatment and the study. All visits to the heath professional sector and the prescribed treatment will have to be collected.

Data will be collected as follows (Appendix 1):

- Prior to randomisation (baseline questionnaire)
- 3-monthly for a year following the start of the trastuzumab (3 monthly questionnaire)
- then every 6 months up to year 2 (6 monthly questionnaire).

13. Concurrent studies

Compatible chemotherapy studies will include Neo-tAnGo, TACT-2, MAPLE and OUTREACH compatible surgical studies will include the proposed EPHOS trial of peri-operative HER2 directed therapy; other compatible studies are those of radiotherapy, or hormonal therapy after completion of primary chemotherapy. The OUTREACH study in the West Anglia Cancer Research Network is compatible. Any concurrent studies not mentioned here needs to be approved as compatible by the trial management group.

REACT is not compatible with Persephone.

14. Statistical considerations

14.1 Sample size determination

The power calculations assume that the disease-free survival (DFS) of the standard treatment of 12 months Trastuzumab will be 80% at 4 years. On this basis, with 5% 1-sided significance and 85% power, a trial randomising 4000 patients in total (2000 in each arm) will have the ability to prove non-inferiority of the experimental arm, defining non-inferiority as 'no worse than 3%' below the control arm 4 year DFS.

14.2 Analysis

Disease-free survival will be calculated from the date of diagnostic biopsy to the date of first relapse or death, if no date of relapse is recorded, or the censor date. The primary outcome of DFS will be carried out on all cause mortality and relapse, and assessed using Kaplan-Meier survival curves. Treatments, with and without adjustment for the stratification and baseline prognostic factors, will be compared using Cox Proportional Hazards analysis. These analyses will be carried out on an intention-to-treat basis. Safety and toxicity will be reported descriptively. Specialist health care economic modelling will be carried out by Professor Christopher McCabe at the University of Leeds. Secondary endpoint of overall survival (OS) will be calculated from the date of diagnostic biopsy to the date of death, or to the censor date. Analyses of all other secondary endpoints will be undertaken using the appropriate statistical analysis tools.
Based on previous documentation of the frequency of the toxicities to be recorded in this trial, the 4000 patients recruited will adequately power the analysis of the secondary outcome of toxicity to detect any clinically relevant differences between treatments, if they exist. Additionally, despite previous studies showing trastuzumab to be well tolerated, we plan to monitor dose intensity in all patients. 4000 patients will be adequate to detect any differences between treatment arms in Dose Intensity.

14.3 PERSEPHONE Data and Safety Monitoring Committee (DSMC)

All data analyses will be supplied to an independent Data and Safety Monitoring Committee which will be asked to give advice on whether the accumulated data from this trial, together with the results from other relevant published trials, justifies the continuing recruitment of further patients. Reports containing recruitment, protocol compliance, safety data and interim analyses of outcomes (not formally tested outside of the trial statistical analysis plan, to be agreed with the DSMC) will be presented to a Data and Safety Monitoring Committee for their review alongside results from other relevant trials. At each of these meetings, the DSMC needs to conclude that there is good compliance and feasibility of treatments (e.g. tolerability of trastuzumab given with the stratified chemotherapy regimens). This Committee will first meet following enrolment of 500 patients or 1 year from the first patient randomised; the exact frequency of subsequent meetings will depend on the rate of accrual, although annual meetings are anticipated.

Although the number of patients required was determined at the 5% level of significance (1-sided), in order to control the overall alpha level, the interim analyses of the primary outcome will be reported to the DSMC using conservative tests with significance determined by a p-value of 0.001. The final analysis will be reported using the standard 5% level of significance (1-sided). Presentation of results to DSMC will include DFS, toxicity, dose-intensity and health care economics, as well as other sub-study outcomes.The DSMC will advise on whether the trial should be stopped prematurely at any time for ethical or safety reasons, including unexpected frequency or severity of toxicity, early indication of inferior outcome in the experimental arm or publication of new data.

14.4 Revised Milestones (July 2009 – protocol Version 3.1)

Persephone will randomise 4000 patients, from an estimated 100 centres in the UK. The aim is to complete accrual within 6 years if possible by maximising the number of UK centres and the speed with which they are activated.

The trial was launched in September 2007 and completion of recruitment is planned for December 2013. The following milestones are based on actual and revised, projected recruitment rates.

- October 2007: First patient randomised
- February 2009: 1st DMSC (18 months of recruitment phase)
- October 2009: Estimated 350 patients recruited
- February 2010: 2nd DMSC (30 months of recruitment phase)
- October 2010: Estimated 1200 patients recruited
- February 2011: 3rd DMSC (42 months of recruitment phase)
- October 2011: Estimated 2100 patients recruited
- February 2012: 4th DMSC (54 months of recruitment phase)
- October 2012: Estimated 3000 patients recruited
- February 2013: 5th DMSC (66 months of recruitment phase)
- December 2013: Estimated 4000 patients recruited, 6th planned DSMC (76 months of recruitment phase).
- Mid-2016: Anticipated planned interim analysis of primary outcome data when all patients have a minimum follow-up of 2.5 years.

15. Pharmacy issues

Neither Trastuzumab nor any other adjuvant treatment is subsidised for the purpose of the ***Persephone*** trial***.*** All drugs should be purchased direct from the usual supplier and must be labelled according to Annex 13.

16. Sponsorship and indemnity

Sponsorship under the EU Directive for clinical trials (May 2004), will require that clinical negligence claims are dealt with using standard procedures in the individual hospital Trust where the patient concerned is treated. The Chief Investigator's NHS Trust Hospital and University (i.e. Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge) will share responsibilities for sponsorship of the ***Persephone*** trial.

Cambridge Hospitals and Cambridge University have an insurance policy in place to provide legal liability compensation for injury caused by participation in this Study in accordance with the Study Protocol. Furthermore, as this is a clinician-initiated study, ABPI guidelines for patient compensation by the pharmaceutical industry will not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available in the event of injury caused by participation or through clinical negligence being proven.

17. Ethical and regulatory issues

17.1 Ethical considerations

The trial will be conducted in full conformance with the principals of the Declaration of Helsinki and in accordance with UK legislation. The study will also adhere to the principles of ICH Good Clinical Practice (GCP) taken from the European Community Guideline CPMP/ICH/135/95.

Copies of the .World Medical Association Declaration of Helsinki. and ICH GCP Guidelines can be obtained from Warwick Medical School Clinical Trials Unit or from the World Medical Association (http://www.wma.net/e/ethicsunit/helsinki.htm) or European Agency for the Evaluation of Medicinal Products website: (http://www.emea.eu.int/pdfs/human/ich/013595en.pdf) respectively.

17.2 Informed consent

The local investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study using the approved patient information sheet, answering any questions the patient may have throughout the study, and sharing any new information that may be relevant to the patient's willingness to continue her participation in the trial in a timely manner.

It is the responsibility of the local investigator to obtain written informed consent from each patient prior to performance of any protocol procedures and prior to the administration of study drug in order to document that the patient is satisfied with her understanding of the risks and benefits of participating in the study and desires to participate.

The consent has to be obtained by the principal investigator, consultant oncologist or by a co-investigator. If the randomising consultant delegates the consent to one of his/her oncology registrar, it remains at his/her responsibility.

17.3 Patient confidentiality

The personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the 1998 Data Protection Act. With the patient's permission, their name will be collected at randomisation. However, patients will be identified using only their unique trial number, initials, date of birth, and hospital number on all case report forms and any correspondence between the ***Persephone*** study office and the study site.

The investigator must maintain documents not for submission to the trials unit (e.g. patients' written consent forms) in strict confidence. In the case of special problems and/or governmental queries, it will be necessary to have access to the complete study records, provided that patient confidentiality is protected.

Warwick Medical School Clinical Trials Unit will maintain the confidentiality of all patient data and will not disclose information by which patients may be identified to any third party, other than those directly involved in the treatment of the patient's breast cancer.

18. Financial matters

Persephone is an investigator-designed and -led trial, which will be funded through project grants. The study has been independently peer reviewed through the National Coordinating Centre for Health Technology Assessment (NCCHTA) which funds the dedicated personnel. There are no funds available for investigator payments or pharmacy fees in this study.

19. Publication policy

The main trial results will be published in the name of the trial in a peer-reviewed journal, on behalf of all collaborators. The manuscript will be prepared by a writing group, appointed from amongst the collaborators. The trials unit and all participating centres and investigators will be acknowledged in this publication. All presentations and publications relating to the trial must be authorised by the Trial Management Group, and the NCCHTA must be given 28 days notice of any presentations or publications arising from the trial, both during recruitment and after analysis.

20. References

1. Piccart-Gebhart MJ, et al. for Trastuzumab Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. NEJM 2005; 353: 1659-1672.
2. Romond EH et al. (joint analysis of NSABP B31, and NCCTG N9831) Trastuzumab plus adjuvant chemotherapy for operable HER2 positive breast cancer. NEJM 2005; 353 1673-1684.
3. Smith I, Procter M, Gelber RD, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet, 2007, 369, 29-36..
4. Slamon D, et al. (BCIRG Study) Phase III Trial comparing AC-T with AC-TH and with TCH in adjuvant treatment of HER2 positive early Breast Cancer Patients: First interim efficacy analysis. Proceedings 28th Annual San Antonio Breast Cancer Symposium. Dec 2005 Abstract No.1.
5. Slamon D et al. BCIRG 006 2nd interim analysis: Phase III Trial comparing AC-T with AC-TH and with TCH in adjuvant treatment of HER2 positive early Breast Cancer Patients Proceedings 29th Annual San Antonio Breast Cancer Symposium. Dec 2006 Abstract No.52.
6. Knoop AS, Knudsen H, Balslev E et al. Retrospective analysis of topoisomerase IIa amplifications and deletions as predictive markers in primary breast cancer patients randomly assigned to cyclophosphamide, methotrexate, and fluorouracil or cyclophosphamide, epirubicin, and fluorouracil: Danish Breast Cancer Cooperative Group. J Clin Oncol. 2005 Oct 20;23(30):7483-90. Erratum in: J Clin Oncol. 2006 Feb 20;24(6):1015.
7. Scandinavian Breast Group Trial 9401: Tanner M, Isola J, Wiklund T et al. Topoisomerase II alpha gene amplification predicts favorable treatment response to tailored and dose-escalated anthracycline-based adjuvant chemotherapy in HER-2/neu-amplified breast cancer: Scandinavian Breast Group Trial 9401. J Clin Oncol. 2006 Jun 1;24(16):2428-36. Epub 2006 May 8.
8. Joensuu H et al. (FinHer Study). Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer NEJM 2006; 354: 809-820.
9. Hind D, Pilgrim H, Ward S. Commentary: Questions about adjuvant trastuzumab still remain. Lancet 2007; 369: 3-5.
10. Anna Wagstaff. PHARE: shining a light for academic research in Europe. Cancer World May-June 2006, p 28-29.
11. Ellis IO, et al. Best Practice No 176. Updated recommendations for HER2 testing in the UK. Journal of Clinical Pathology 2004; 57; 233-237
12. Tan-Chui E, Yothers G, Romond R et al. Assessment of cardiac dysfunction in a randomised trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-over-expression breast cancer: NSABP B-31. J Clin Oncol 2005:7811-7819.
13. Poole CJ, Earl HM, Hiller L, Dunn JA, et al. Epirubicin and Cyclophosphamide, Methotrexate, and Fluorouracil as Adjuvant Therapy for Early Breast Cancer. N Engl J Med, 2006; 355 : 1851-62
14. Coombes RC, Bliss JM, Wils J et al. Adjuvant cyclophosphamide, methotrexate, and fluorouracil versus fluorouracil, epirubicin, and cyclophosphamide chemotherapy in premenopausal women with axillary node-positive operable breast cancer: results of a randomized trial. The International Collaborative Cancer Group. J Clin Oncol. 1996 Jan;14(1):35-45.
15. Poole CJ, Howard HC, Hiller L, et al. A prospective evaluation of pulmonary, cardiac, and hepatic function (fn) in 'tAnGo': a randomized phase III trial of gemcitabine (G) in paclitaxel (T)-containing, epirubicin/cyclophosphamide (EC)-based, adjuvant chemotherapy (CT) for early stage breast cancer. Proc ASCO, J Clin Oncol 2004, 23; Abstract 821.
16. Mamounas EP, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol. 2005;23(16):1-11.
17. Roché H, Fumoleau P, Spielmann M, et al. Sequential Adjuvant Epirubicin-Based and Docetaxel Chemotherapy for Node-Positive Breast Cancer Patients: The FNCLCC PACS 01 Trial. J Clin Oncol 2006; 24(36):5664-71.
18. Martin M, Pienkowski T, Mackey J et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med. 2005 Jun 2;352(22):2302-13
19. Coombes RCC, Kilburn LS, Snowdon CF et al. Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet 2007; 369: 559-70.
20. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart G. Textbook: Methods for the Economic Evaluation of Health Care Programmes (Third Edition), Oxford University Press, June 2005.

21. Brooks RG, et al. EuroQoL: health-related quality of life measurement. Results of the Swedish questionnaire exercise. Health Policy 1991;18(1):37-48.
22. Kind P, Dolan P. The effect of past and present illness experience on the valuations of health states. Med Care. 1995 ; 33(4 Suppl) : AS255-63.
23. Manca A, Hawkins N, Sculpher MJ, Estimating Mean QALYs in Trial-based Cost-effectiveness Analysis: The Importance of Controlling for Baseline Utility, Health Economics 2006, 14(5), 487-96.
24. Brouwer WB, Niessen LW, Postma MJ, and Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analyses. BMJ 2005; 331(7514):446-8.
25. Claxton K, Sculpher M, Culyer A, McCabe C, et al. Discounting and cost-effectiveness in NICE - stepping back to sort out a confusion. Health Econ. 2006 ;15(1):1-4.
26. NICE Methods Guide, 2004
27. Weinstein MC et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices--Modeling Studies. Value Health. 2003; 6(1) : 9-17.
28. Earl HM, Vallier A, Hiller H, Fenwick N, Iddawela M, Hughes-Davies L, Provenzano E, McAdam, K, Hickish T, Caldas C, and for NeotAnGo Investigators Neo-tAnGo. Neo-tAnGo: A neoadjuvant randomized phase III trial of epirubicin/cyclophosphamide and paclitaxel ± gemcitabine in the treatment of women with high-risk early breast cancer (EBC): First report of the primary endpoint, pathological complete response (pCR) (2009).ASCO Meeting Abstracts 27: 522.

Appendix 1: Timetable of events and investigations for *Persephone*

Schedule of investigations during on-study phase

Event	**Prior to randomisation** (Baseline)	**Trastuzumab treatment visit** Every 3 months for a year after starting trastuzumab treatment ***Patients on the research arm MUST follow the same follow-up schedule as those on the standard arm***	**Follow-up visits** Every 6 months year 2. Annually thereafter
Informed consent for trial	X		
ER status	X		
HER2 status	X		
Full blood count	X		
Biochemical screen	X		
Chest X-ray (or Chest CT if standard practice)	Additional scans if suspicion of metastases		
Whole body scintigraphy and liver ultrasound or abdominal CT scan			
Medical history	X		
Physical examination, weight.	X[a]	X[a]	X[a]
LVEF assessment	Done as per standard practice	X[b]	
ECOG performance status	X	X	X
Quality of Life assessment	X[c]	X[d]	X[e]
Healthcare resource used assessment	X[c]	X[d]	X[e]
Serious Adverse events		X	
Survival / recurrence disease		X	X

a Includes clinical follow-up, and questioning patients regarding symptoms of progression or recurrent breast cancer.
b To be carried out at 6 months i.e. after cycle 9, at 9 months i.e. after cycle 13 or 14 and where possible at 12 months i.e. after cycle 18.
c Patient to complete the baseline questionnaire.
d Patient to complete the 3 monthly questionnaire.
e Patient to complete the 6 monthly questionnaire.

Appendix 2: TNM Staging System for Breast Cancer

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

Definitions of TNM

Primary Tumour (T)

- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Tis Carcinoma *in situ*: intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumour
- T1 Tumour ≤2 cm in greatest dimension
  - T1mic Micro-invasion ≤0.1cm in greatest dimension
  - T1a Tumour >0.1 but ≤0.5 cm or less in greatest dimension
  - T1b Tumour >0.5 cm but ≤1 cm in greatest dimension
  - T1c Tumour >1 cm but ≤2 cm in greatest dimension
- T2 Tumour >2 cm but ≤5 cm in greatest dimension
- T3 Tumour >5 cm in greatest dimension
- T4 Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below.
  - T4a Extension to chest wall, not including pectoralis muscle
  - T4b Edema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast
  - T4c Both (T4a and T4b)
  - T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumor is classified according to the size of the tumour.

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed (for example, previously removed)
- N0 No regional lymph node metastasis
- N1 Metastasis to movable ipsilateral axillary lymph node(s)
- N2 Metastasis to ipsilateral axillary lymph node(s) fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the absence of clinically evident* axillary lymph node metastasis
  - N2a Metastasis in ipsilateral axillary lymph nodes fixed (or matted) to one another or to other structures
  - N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes *and* in the absence of clinically evident axillary lymph node metastasis
- N3 Metastasis to ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the presence of clinically evident axillary or internal mammary lymph node involvement; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  - N3a Metastasis in ipsilateral infraclavicular lymph node(s)
  - N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  - N3c Metastasis in ipsilateral supraclavicular lymph node(s)

*** Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.**

Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Stage grouping

STAGE GROUPING	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0	N1*	M0
	T1	N1**	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2*	M0
	T1	N2**	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Appendix 3: ECOG performance status

Grade	Description
0	Normal activity: asymptomatic
1	Symptomatic: fully ambulatory
2	Symptomatic: in bed < 50% of time
3	Symptomatic: in bed > 50% of time - not bedridden
4	100% bedridden

Appendix 4 : The Stages of Heart Failure – NYHA Classification:

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Appendix 5: Chemotherapy Regimens Commonly Used in the UK

- **ECMF: Epirubicin -> Cyclophosphamide / Methotrexate / 5-Flurouracil (13)**

Epirubicin (E) 100mg/m^2 IV, day1 every 3 weeks for 4 cycles. Then CMF Cyclophosphamide (C) 600mg/m^2 D 1&8 IV or 100mg/m^2 PO D1-14; Methotrexate (M) 40mg/m^2 D1&8 IV and 5-Fluorouracil (F) 600mg/m^2, day1 and 8 every 4 weeks for 4 cycles. OR: Epirubicin (E) 100mg/m^2 IV, day1 every 3 weeks for 4 cycles. Followed by CMF Cyclophosphamide (C) 750mg/m^2 D 1, IV; Methotrexate (M) 50mg/m^2 D1 IV and 5-Fluorouracil (F) 600mg/m^2, day1 every 3 weeks for 4 cycles (Scottish ECMF used in the NEAT trial).

- 4 weekly ACMF : 5-Fluorouracil / Doxorubicin / **Cyclophosphamide**

Doxorubicin (A) 26mg/m^2 IV, day1 and 130 mg/m2 **Cyclophosphamide (C)**, 26 mg/m2 **Methotrexate (M)**, and 600 mg/m2 **5-Fluorouracil (F)**on days 1 and 8 **every 3 weeks for 6 cycles.**

- 4 weekly FEC : FEC: 5-Fluorouracil / Epirubicin / Cyclophosphamide (14)

5-Fluorouracil 600mg/m^2 IV; Epirubicin 50-100mg/m^2 IV and Cyclophosphamide 600mg/m^2 IV day1 every 3 weeks for 6 cycles or FEC day1 and 8 every 4 weeks for 6 cycles.

- **3 weekly FEC : FEC: 5-Fluorouracil / Epirubicin / Cyclophosphamide (14)**

FEC :5-Fluorouracil 600mg/m^2 IV; Epirubicin 50-100mg/m^2 IV and Cyclophosphamide 600mg/m^2 IV day1 every 3 weeks for 6 cycles.

- **3 weekly FEC : FEC: 5-Fluorouracil / Epirubicin / Cyclophosphamide**

FEC :5-Fluorouracil 500mg/m^2 IV; Epirubicin 50mg/m^2 IV and Cyclophosphamide 500 mg/m^2 IV day1 every 3 weeks for 6 cycles.

- **3 weekly FEC – FEC100 (French Adjuvant Study Group 05) : FEC: 5-Fluorouracil / Epirubicin / Cyclophosphamide**

FEC :5-Fluorouracil 500mg/m^2 IV; Epirubicin 100mg/m^2 IV and Cyclophosphamide 500 mg/m^2 IV day1 every 3 weeks for 6 cycles.

- 3 weekly FAC : FAC: 5-Fluorouracil / Doxorubicin / **Cyclophosphamide**

FEC :5-Fluorouracil 500mg/m2 IV; Doxorubicin 50 mg/m2 IV and Cyclophosphamide 500 mg/m2 IV day1 every 3 weeks for 6 cycles.

- **EC-P: Epirubicin / Cyclophosphamide → Paclitaxel (15,16)**

Epirubicin (90 mg/m^2 by slow push into fast drip) and cyclophosphamide (600 mg/m^2 by slow push infusion), both day 1, every 3 weeks for 4 cycles. Followed by paclitaxel (P) (175 mg/m^2 by 3 hour infusion), day 1, every 3 weeks for 4 cycles. (as in the tAnGo trial).

- **FEC-docetaxel (PACS-01): 5-Fluorouracil / Epirubicin / Cyclophosphamide → Docetaxel (17)**

5-Fluorouracil 500mg/m^2 IV ; Epirubicin 100 mg/m^2 IV and cyclophosphamide 500 mg/m^2 , FEC day1 every 3 weeks for 3-4 cycles or FEC day1 and 8 every 4 weeks for 3-4 cycles. Then docetaxel (D) 100 mg/m^2, day 1, every 3 weeks for 3-4 cycles.

- **TAC: Docetaxel/ Doxorubicin / Cyclophosphamide (18)**

Docetaxel (75 mg/m^2), Doxorubicin (A) (50mg/m^2) and Cyclophosphamide (500mg/m^2), IV day1 every 3 weeks for 6 cycles.

- **AC-Docetaxel: Doxorubicin / cyclophosphamide → Docetaxel (4,5)**

Doxorubicin 60mg/m^2, and cyclophosphamide 600mg/m^2 every 3 weeks x 4 cycles, then docetaxel 100mg/m^2 every 3 weeks for 4 cycles.

- **EC-Docetaxel: Doxorubicin / cyclophosphamide → Docetaxel**

Epirubicin 60mg/m^2, and cyclophosphamide 600mg/m^2 every 3 weeks x 4 cycles, then docetaxel 100mg/m^2 every 3 weeks for 4 cycles.

- **TCH: Docetaxel / carboplatin / Herceptin® (4,5)**

Docetaxel 75mg/m2 with carboplatin AUC x 6, every 3 weeks for 6 cycles.

<u>Taxane → Anthracycline reverse sequence chemotherapy</u>

- **Docetaxel – FEC (reverse PACS-01): Docetaxel → 5-Fluorouracil / Epirubicin / Cyclophosphamide**

Docetaxel (D) 100 mg/m^2, day 1, every 3 weeks for 3-4 cycles. Then 5-Fluorouracil 500mg/m^2 IV ; Epirubicin 100 mg/m^2 IV and cyclophosphamide 500 mg/m^2 , FEC day1 every 3 weeks for 3-4 cycles or FEC day1 and 8 every 4 weeks for 3-4 cycles.

Appendix 7: The PHARE Trial

PHARE
Protocol of Herceptin® Adjuvant with Reduced Exposure: A randomised comparison of 6 months *vs* 12 months in all women receiving adjuvant Herceptin®

http://www.clinicaltrials.gov/ct/show/NCT00381901
http://www.e-cancer.fr/Recherche/Recherche-clinique-Biostatistiques/Essai-PHARE

RATIONALE OF THE STUDY

The Institut National du Cancer (INCa) is the sponsor of a randomised clinical trial aimed at evaluating the non-inferiority, in terms of disease-free survival, of a reduction of exposure to Herceptin®: 6 months *versus* 12 months after stratification by the mode of administration of chemotherapy (concomitant or sequential). This trial aims at being pragmatic, including a very large number of patients, with a follow-up as close as possible to that of routine clinical practice. Participation in the trial is proposed to all French investigators and healthcare centres treating patients with breast cancer. The objective is to include all patients receiving an adjuvant treatment with Herceptin® in order to recruit 7000 patients as soon as possible.

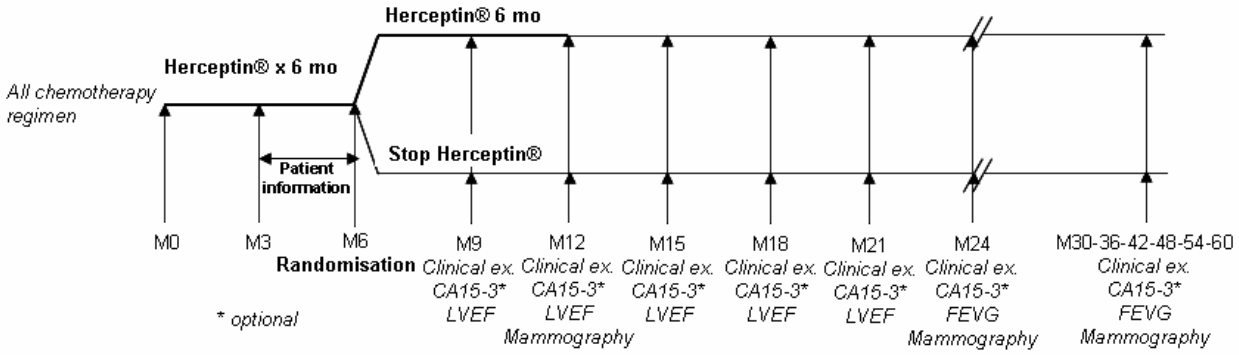
OBJECTIVES OF THE TRIAL

Primary objective: To compare the effects of 6 months *versus* 12 months of treatment with Herceptin® in terms of disease-free survival in patients who have already been treated with Herceptin® for 6 months.

Secondary objectives:
To compare:
- Cardiotoxicity between the two arms of treatment.
- The effects on disease-free survival of a concomitant administration of Herceptin®/ chemotherapy and a sequential administration.
- Cardiotoxicity between the 2 modes of administration (concomitant and sequential).

Ancillary study:
- To investigate the link between HER2 polymorphism and disease-free survival/cardiotoxicity.

STUDY DESIGN



TRIAL ORGANISATION

Principal Investigator - **Pr Xavier Pivot** - Centre Hospitalier Universitaire de Besançon, Service d'Oncologie Médicale, 25030 BESANCON cedex - France
Phone: +33 (0)3 81 66 93 86 - Fax: + 33 (0)3 81 66 88 58 - Xavier.pivot@univ-fcomte.fr

Trial Management - **Iris Pauporté, PhD** - Institut National du Cancer, 52 avenue Morizet, 92513 BOULOGNE BILLANCOURT - France
Phone: +33 (0)1 41 10 14 86 – Fax: + 33 (0) 1 41 10 14 89 - ipauporte@institutcancer.fr

Statistician - **Xavier Paoletti, PhD** - Institut National du Cancer, 52 avenue Morizet, 92513 BOULOGNE BILLANCOURT - France
Phone: +33 (0)1 41 10 14 87 – Fax: + 33 (0) 1 41 10 14 89 - xpaoletti@institutcancer.fr