The Lancet Oncology

Quality of life results in the UK TACT2 Trial of accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer: a multicentre, phase 3, open-label, randomised, controlled trial (CRUK/05/19)

--Manuscript Draft--

Manuscript Number:	THELANCETONCOLOGY-D-23-00571R3
Article Type:	FAST-TRACK Article (Clinical Trials)
Keywords:	quality of life; breast cancer; patient-reported outcomes; adjuvant chemotherapy
Corresponding Author:	Galina Velikova, PhD MD University of Leeds Leeds, UNITED KINGDOM
First Author:	Galina Velikova, PhD MD
Order of Authors:	Galina Velikova, PhD MD
	Joanne S Haviland, MSc
	Charlotte Emery
	Peter Barrett-Lee
	Helena Earl
	David Bloomfield
	A Murray Brunt
	Peter Canney
	Robert Coleman
	Mark Verrill
	Andrew Wardley, MD
	Gianfillipo Bertelli
	Paul Ellis
	Robert Stein, FRCP
	Judith Bliss, MSc
	David Cameron, MD
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	Background: Adjuvant chemotherapy for early breast cancer (EBC) improves outcomes but its toxicity impacts patients' quality of life (QOL). UK TACT2 trial investigated whether accelerated epirubicin (aE) improves time-to-recurrence (TTR) and if oral capecitabine is non-inferior to cyclophosphamide, methotrexate and fluorouracil (CMF) for efficacy with less toxicity. Results showed no aE benefit and capecitabine was non-inferior. As part of the QOL sub-study we report here the impact of chemotherapies on psychological distress, physical symptoms and functional domains. Methods: TACT2 was multicentre, phase 3, randomised, controlled trial, which enrolled patients aged ≥18 years from 129 UK centres with histologically confirmed node-positive or high-risk node-negative operable breast cancer, following complete excision, and due to receive adjuvant chemotherapy. Patients were randomised to four cycles of 100 mg/m2 epirubicin either every 3 weeks (standard epirubicin) or every 2 weeks with 6 mg pegfilgrastim on day 2 of each cycle (accelerated epirubicin), followed by four 4-week cycles of either classic cyclophosphamide, methotrexate, and fluorouracil (CMF; 600 mg/m2 cyclophosphamide intravenously on days 1 and 8 or 100 mg/m2 orally on

	days 1–14; 40 mg/m2 methotrexate intravenously on days 1 and 8; and 600 mg/m2 fluorouracil intravenously on days 1 and 8 of each cycle) or four 3-week cycles of 2500 mg/m2 capecitabine (1250 mg/m2 given twice daily on days 1–14 of each cycle). The randomisation schedule was computer generated in random permuted blocks, stratified by centre, number of nodes involved (none vs 1-3 vs ≥4), age (≤50 vs >50 years), and planned endocrine treatment (yes/no). The primary endpoint was TTR which has been reported. QOL was one of the secondary outcomes. All patients from a subset of 44 centres were invited to complete QOL questionnaires (Hospital Anxiety Depression Scale, EORTC QLQ-C30, EORTC QLQ-BR23) at baseline, end aE/E, end CMF/capecitabine, 12 and 24-months post-randomisation. QOL substudy pre-specified two co-primary QOL outcomes: Overall QOL (already reported) and HADS-Total score. Pre-specified secondary QOL outcomes were EORTC QLQ-C30 subscales physical function, role function, fatigue and EORTC-BR23 subscales sexual function and systemic therapy side-effects. QOL sub-study needed 1000 patients to provide complete case data on 800-850 patients at 12-months (assuming 15-20% attrition) and allow analysis of 4 separate groups of 200-213 patients with 92%-94% power to detect a difference of >20% in any proportions (α=0.01). Intention-to-treat analysis included cross-sectional comparisons (Mann-Whitney non-parametric tests), change scores comparsions (ANCOVA adjusting for baseline score) and generalised estimating equations models. This trial is registered with ISRCTN, number 68068041, and with ClinicalTrials.gov, number NCT00301925. Findings: From Dec 16th, 2005-Dec 5th, 2008, 4391 patients (20 male) were randomised in TACT2 trial, 1281(86%, 8 male) patients of 1493 approached consented to the QOL sub-study. Median follow-up 85.6 month (IQR 80.6-95.9). Analysis was performed on complete QOL dataset (of Sept 15th, 2011) when all participants had passed 24-month timepoint. Pre-randomisation questionnaires were completed by 1172/1281 (91%) patients, 1179/1281 (92%) completed at least one post-randomisation questionnaire. For HADS (co-primary QOL outcome0, the only differences were end-of-treatment scores worse for CMF vs capecitabine: HADS-Depression (p=0.0048) and HADS-Total change score (p=0.0093). aE led to worse physical (p=0.0065), role function (p<0.0001) (but not sexual function, p=0.36), fatigue (0.00018), systemic side effects (0.00012) compared with E during treatment, but the impact did not persist. Worse physical (0.0048) and sexual function (0.0053), fatigue (<0.0001) and systemic side-effects (<0.0001) were seen for CMF vs capecitabine end-of-tretament. These differences persisted at 12 and 24-months. Interpretation: aE was associated with worse QOL compared with E but only during treatment. These findings will help patients/clinicians make an informed choice about accelerated chemotherapy. CMF had worse QOL effects than capecitabine, persistent for 24-months. The favourable capecitabine QOL compared with CMF supports its use as an adjuvant option post-neoadjuvant chemotherapy in patients with triple-negative breast cancer. Funding. Cancer Research UK, Amgen, Pfizer, and Roche.

-Responses to Editor's comments
Thank you, please see our responses in red below.

Editor's comments:

1. **RESEARCH IN CONTEXT:** Please ensure that this panel should adheres to the following guidelines:
    a. Evidence before this study

        This section should include a description of all the evidence that the authors considered before undertaking this study (ie, a description of similar published research and the study's niche). Authors should state: the sources (databases, journal or book reference lists, etc) searched; the criteria used to include or exclude studies (including the exact start and end dates of the search), which should not be limited to English language publications; the search terms used; the quality (risk of bias) of that evidence; and the pooled estimate derived from meta-analysis of the evidence, if appropriate (ie, the search used to identify similar studies should be described). A summary of what the existing evidence shows should also be included.

Following the recommendation above proved challenging in this setting and I really struggled to do it. This was due to the fact that I was trying to summarise two clinical questions (dose-dense chemotherapy and oral chemotherapy) and their impact on QOL over 2 decades. Doing Pubmed searches yields tens of thousands of publications, mostly irrelevant. So, I opted to focus on published systematic review of papers with QOL measurement, plus I checked the RCTs included in the 2019 meta-analysis of dose-dense chemotherapy to see if they had published any QOL data (which they hadn't) (pages 4-5). I hope this looks satisfactory. As I included the systematic reviews in this box, I went back to add them to the main text of the paper too (see pages 6 and 14)).

    b. Added value of this study

        Authors should summarise here how their findings add value to the existing evidence. IMPORTANT: Please do NOT reiterate the results (eg, do not include data) or describe your study approach (this is already covered by the abstract), but rather explain how the findings extend knowledge in the field and/or address unanswered questions or controversies.

This paragraph has been re-worded, and hopefully meets the expectations (page 5).

    c. Implications of all the available evidence

        Authors should state the implications for practice or policy and future research of their study combined with existing evidence.

Re-worded to include the implications of CMF findings (page 5).

2. **SUMMARY:** Please ensure the Summary includes the following:
    a. Methods: A brief summary of the key inclusion criteria (including age limit, disease status and histologies permitted, performance status, and if second line or beyond, criteria regarding previous lines of treatment) - Added
    b. Methods: Details of the regimens used (including dose, schedule and route of administration)- Added
    c. Methods: Details of how randomisation was done (eg, allocation concealment; nature of blinding, if any; how sequence was generated; stratification factors, etc). -Added
    d. Methods: An explicit description of the actual primary endpoint with QoL listed as a secondary/exploratory endpoint. Added
    e. Methods: The nature by which analyses were done (eg, intention to treat, per protocol). Added
    f. Methods: The trial registration number. Added
    g. Methods: The status of the trial – is it ongoing/still enrolling/is this an interim analysis, etc? Analysis was performed on the complete dataset (dated Sept 15th, 2011) when all participants had passed the 24 month timepoint.
    h. Findings: Exact dates of recruitment and median follow-up (IQR) for the analyses presented. The exact dates of recruitment were already in the Summary. I added the median follow-up (IQR) for TACT2 but I don't think this is relevant because the QOL sub-study data collection ended long before the main trial follow-up. I added this sentence which, I think, describes better the situation "Analysis was performed on complete dataset (dated Sept 15th, 2011) when all participants had passed the 24 month timepoint".
    i. Findings: Please add a breakdown of sex/gender to the Summary Findings (assuming these data have been collected) Added

    Please note that all results reported in the Summary need to be reported in the main text. I slightly changed the reporting of the findings to include only the pre-specified scales with p values.

    See recent issues of the journal for examples. Accuracy and completeness here are essential.

3. Methods: Outcomes: Please ensure the following items are included:
    a. Definition of the primary endpoint (ie, DFS). Added
    b. Definition of all secondary endpoints. Added
    c. Please ensure any prespecified exploratory endpoints are clearly described as such, and move any post-hoc outcomes to the Statistical analysis section. Added

4. Methods: Statistical analysis. Please ensure the following items are included:
    a. A sentence or two on the original sample size calculation. Added

----------End of comments----------

Quality of life results in the UK TACT2 Trial of accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer: a multicentre, phase 3, open-label, randomised, controlled trial (CRUK/05/19)

Galina Velikova, James P Morden*, Joanne S Haviland, Charlotte Emery, Peter Barrett-Lee, Helena Earl, David Bloomfield, Adrian Murray Brunt, Peter Canney 7, Robert Coleman, Mark Verrill, Andrew Wardley, Gianfilippo Bertelli, Paul Ellis, Rob Stein, Judith M Bliss, David Cameron on behalf of the TACT2 Trial Management Group

Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK (Prof G Velikova FRCP PhD)

Institute of Cancer Research Clinical Trials and Statistics Unit, Institute of Cancer Research, London, UK (J P Morden MSc, J S Haviland MSc, C Emery MSc, Prof J M Bliss MSc)

Department of Oncology, Velindre University NHS Trust, Cardiff, UK (Prof P Barrett-Lee MD)

Department of Oncology, University of Cambridge and NIHR Cambridge Biomedical Research Centre, UK (Prof H Earl PhD)

Department of Oncology, University Hospitals Sussex, Brighton, UK (Prof DJ Bloomfield FRCR, Prof G Bertelli PhD)

School of Medicine, University of Keele, Keele & Department of Oncology, University Hospitals of North Midlands, Stoke-on-Trent, UK (Prof A M Brunt FRCP)

Beatson Oncology Center, Glasgow, UK (P Canney MD)

Department of Oncology, Weston Park Hospital, Sheffield, UK (Prof R Coleman FRCP)

Department of Oncology, Northern Centre for Cancer Care, Freeman Hospital, Newcastle, UK (M Verrill FRCP)

Outreach Research & Innovation Group, Manchester, UK (Prof A Wardley MD)

King's College London and Leaders in Oncology Care (LOC) London, UK (Prof P Ellis FRCP)

University College London Hospitals, London, UK (Prof R Stein FRCP)

University of Edinburgh Cancer Centre, Institute of Genetics and Cancer, Western General Hospital, Edinburgh, UK (Prof D Cameron MD)

*deceased

Correspondence to:
Prof Galina Velikova
Leeds Institute of Medical Research at St James's, University of Leeds
Leeds Cancer Centre, St James's University Hospital, Bexley wing
Beckett street
Leeds, LS9 7TF, UK
g.velikova@leeds.ac.uk

Summary

Background:
Adjuvant chemotherapy for early breast cancer (EBC) improves outcomes but its toxicity impacts patients' quality of life (QOL). UK TACT2 trial investigated whether accelerated epirubicin (aE) improves time-to-recurrence (TTR) and if oral capecitabine is non-inferior to cyclophosphamide, methotrexate and fluorouracil (CMF) for efficacy with less toxicity. Results showed no aE benefit and capecitabine was non-inferior. As part of the QOL sub-study we report here the impact of chemotherapies on psychological distress, physical symptoms and functional domains.

Methods:
TACT2 was multicentre, phase 3, randomised, controlled trial, which enrolled patients aged ≥18 years from 129 UK centres with histologically confirmed node-positive or high-risk node-negative operable breast cancer, following complete excision, and due to receive adjuvant chemotherapy. Patients were randomised to four cycles of 100 mg/m2 epirubicin either every 3 weeks (standard epirubicin) or every 2 weeks with 6 mg pegfilgrastim on day 2 of each cycle (accelerated epirubicin), followed by four 4-week cycles of either classic cyclophosphamide, methotrexate, and fluorouracil (CMF; 600 mg/m2 cyclophosphamide intravenously on days 1 and 8 or 100 mg/m2 orally on days 1–14; 40 mg/m2 methotrexate intravenously on days 1 and 8; and 600 mg/m2 fluorouracil intravenously on days 1 and 8 of each cycle) or four 3-week cycles of 2500 mg/m2 capecitabine (1250 mg/m2 given twice daily on days 1–14 of each cycle).

The randomisation schedule was computer generated in random permuted blocks, stratified by centre, number of nodes involved (none vs 1-3 vs ≥4), age (≤50 vs >50 years), and planned endocrine treatment (yes/no). The primary endpoint was TTR which has been reported. QOL was one of the secondary outcomes.

All patients from a subset of 44 centres were invited to complete QOL questionnaires (Hospital Anxiety Depression Scale, EORTC QLQ-C30, EORTC QLQ-BR23) at baseline, end aE/E, end CMF/capecitabine, 12 and 24-months post-randomisation. QOL substudy pre-specified two co-primary QOL outcomes: Overall QOL (already reported) and HADS-Total score. Pre-specified secondary QOL outcomes were EORTC QLQ-C30 subscales physical function, role function, fatigue and EORTC-BR23 subscales sexual function and systemic therapy side-effects. QOL sub-study needed 1000 patients to provide complete case data on 800-850 patients at 12-months (assuming 15-20% attrition) and allow analysis of 4 separate groups of 200-213 patients with 92%-94% power to detect a difference of >20% in any proportions (α=0.01). Intention-to-treat analysis included cross-sectional comparisons (Mann-Whitney non-parametric tests), change scores comparsions (ANCOVA adjusting for baseline score) and generalised estimating equations models. This trial is registered with ISRCTN, number 68068041, and with ClinicalTrials.gov, number NCT00301925.

Findings: From Dec 16th, 2005-Dec 5th, 2008, 4391 patients (20 male) were randomised in TACT2 trial, 1281(86%, 8 male) patients of 1493 approached consented to the QOL sub-study. Median follow-up 85.6 month (IQR 80.6-95.9). Analysis was performed on complete QOL dataset (of Sept 15th, 2011) when all participants had passed 24-month timepoint. Pre-

randomisation questionnaires were completed by 1172/1281 (91%) patients, 1179/1281 (92%) completed at least one post-randomisation questionnaire. For HADS (co-primary QOL outcome0, the only differences were end-of-treatment scores worse for CMF vs capecitabine: HADS-Depression (p=0.0048) and HADS-Total change score (p=0.0093). aE led to worse physical (p=0.0065), role function (p<0.0001) (but not sexual function, p=0.36), fatigue (0.00018), systemic side effects (0.00012) compared with E during treatment, but the impact did not persist. Worse physical (0.0048) and sexual function (0.0053), fatigue (<0.0001) and systemic side-effects (<0.0001) were seen for CMF vs capecitabine end-of-tretament. These differences persisted at 12 and 24-months.

Interpretation: aE was associated with worse QOL compared with E but only during treatment. These findings will help patients/clinicians make an informed choice about accelerated chemotherapy. CMF had worse QOL effects than capecitabine, persistent for 24-months. The favourable capecitabine QOL compared with CMF supports its use as an adjuvant option post-neoadjuvant chemotherapy in patients with triple-negative breast cancer.

Funding. Cancer Research UK, Amgen, Pfizer, and Roche.

Research in context

Evidence before this study

At the time this study was designed in 2004, the optimal adjuvant chemotherapy treatment for early breast cancer had not been established. Some trials showed improved efficacy with accelerated or dose-dense chemotherapy (shorter intervals between chemotherapy cycles by using growth factor). This approach was becoming the standard of care in parts of the world, without robust data on the impact of the accelerated treatment on patients' quality of life (QOL). At the time, one of the standard UK regimens for moderate risk early breast cancer was epirubicin (E) followed by cyclophosphamide, methotrexate, and fluorouracil (CMF). The toxicity of this treatment was a concern, with observations from two other trials of treatment-related deaths during CMF. TACT2 trial was designed to investigate whether use of accelerated E (aE) would improve time to tumour recurrence and whether using oral capecitabine instead of CMF would be non-inferior for efficacy but better tolerated in terms of toxicity and impact on QOL.

In 2003, a systematic review of health-related QOL measuremen in breast cancer (Goodwin P et al, 2003) identified only 6 randomised controlled trials of adjuvant chemotherapy in breast cancer with QOL results, suggesting a transient negative impact, especially of more aggressive treatments (anthracyclines, taxanes). An update of this systematic review in 2011 (Lemieux J et al, 2011) , reported further 16 trials comparing different chemotherapy treatments, confirming a decline in QOL during treatment with recovery by 12 months. There was only one trial of dose-dense chemotherapy (Del Mastro et al, 2002) which showed worse psychological distress during dose-dense treatment with recovery by 6 months. One non-inferiority trial comparing classical CMF with an oral fluoropyrimidine (uracil-tegafur) showed similar efficacy but better QOL with oral chemotherapy (Watanabe T et al, 2009).

TACT2 trial primary outcome showed no benefit for aE and confirmed non-inferiority of capecitabine over CMF in time to tumour recurrence. The results confirmed better tolerability of capecitabine over CMF (with standard toxicity reporting by clinicians), with worse overall quality of life (primary QOL outcome) reported by patients on CMF at the end of treatment and up to 24-months. aE led to worse overall QOL during the treatment, which was not sustained by the end of chemotherapy.

In 2019, an individual patient-level meta-analysis of dose-dense chemotherapy (which included TACT2 data) found modest benefits of 13% reduction in mortality and 14% reduction in cancer recurrences for accelerated chemotherapy. However, the long-term QOL effects of the dose-dense chemotherapy were less well known. Only one trial of dose-dense chemotherapy included QOL measures, reporting worse QOL impact during and at end-of-treatment but the trial did not evaluate QOL in the longer term (Foukakis T et al 2016).

Here, we report the detailed TACT2 quality of life sub-study, including analysis of physical symptoms and functional impact, to build a comprehensive picture of patient experiences during adjuvant chemotherapy and in the following 24-months.

Added value of this study

This study confirmed the negative impact of accelerated chemotherapy during the treatment with adiditonal information of the range of affected QOL areas (physical and role functions, fatigue and self-reported side-effects). To the best of our knowledge, for the first time we demonstrated that this impact did not last and was no longer detectable 12-months after starting chemotherapy. CMF was associated with worse physical side effects than capecitabine and led to worse physical, role and social functioning. Importantly, we showed that these differences persisted up to 24-months.

Implications of all the available evidence

The meta-analysis of adjuvant dose-dense chemotherapy established this approach as a standard of care. Our detailed QOL analysis provides patients and clinicians with details on the range and extent of the additional symptom burden and QOL impact, and importantly confirm that this additional burden resolves within 12-months of starting therapy.

The lasting side-effects and functional impact of CMF adds to the clinical reasons for further reducing its use as part of adjuvant treatments for early breast cancer. The favourable symptom burden and functions data on capecitabine supports its increased use as 'rescue' adjuvant treatment after neo-adjuvant chemotherapy with residual disease in triple negative patients.

Introduction

Improvements in outcomes for women diagnosed with early breast cancer led to an increased emphasis on evaluating toxicity of the adjuvant chemotherapy regimens and the longer-term impact on patients' health-related quality of life (QOL). This approach is especially important when more intensive treatments result in small survival gains. Even in the era of genomic testing [1], oncologists must balance toxicity and estimated benefits to help patients decide about adjuvant chemotherapy when the majority of patients would not individually benefit. For example, QOL results from the TACT trial showed that taxane-containing chemotherapy impaired global QOL and affected more QOL domains during treatment than anthracycline-based chemotherapy. However, most QOL parameters returned to baseline 2-years post-treatment[2]. The patient-reported data is acknowledged to play a key role in shared decision-making about adjuvant chemotherapy.

In 2003, a systematic review of health-related QOL measuremen in breast cancer identified only 6 randomised controlled trials of adjuvant chemotherapy in breast cancer, suggesting a transient negative impact, especially of more aggressive treatments (anthracyclines, taxanes)[3]. An update of this systematic review in 2011[4], reported further 16 trials comparing different chemotherapy treatments, confirming a decline in QOL during treatment with recovery by 12 months. However, there was only one reported trial of dose-dense chemotherapy with QOL measurement which showed worse psychological distress during dose-dense treatment with recovery by 6 months[5].

TACT2 was a multicentre, phase III, randomised controlled trial of adjuvant non-taxane chemotherapy in women with early breast cancer, using 2x2 factorial design. The control group was sequential epirubicin(E)-CMF chemotherapy (based on NEAT trial results)[6]. Two hypotheses were tested: 1) accelerating epirubicin (aE) gives superior benefits in time to tumour recurrence and 2) using oral capecitabine instead of CMF would be non-inferior for patient outcomes but advantageous with less toxicity and better QOL. Primary outcome results showed no benefit for aE and confirmed non-inferiority of capecitabine to CMF in time to tumour recurrence[7]. Only the primary QOL outcome (Global Health Status/QOL) was reported in the main publication. The results confirmed better tolerability of capecitabine over CMF, with worse global QOL observed in patients on CMF at treatment end, and importantly, the difference persisting at 12 and 24-months, suggesting long-term negative effects of CMF. In the E vs aE comparison, Global Health Status/QOL was worse in aE during the treatment, but did not persist afterwards. We now report the impact of the treatments on a wider range of patient symptoms and experiences (psychological distress, physical, role and social functioning) to understand the reasons for the global QOL differences and to provide detailed information to future patients. This research question is important and relevant to current clinical practice, as the meta-analysis of dose-dense chemotherapy found only modest benefits (13% mortality reduction; 14% reduction in cancer recurrences). However, the short and long-term QoL effects of dose-dense chemotherapy are less well known, highlighting the need for patient-reported data to inform clinician-patient communication and shared decisions-making [8]. Furthermore, current practice includes the use of capecitabine post-neoadjuvant chemotherapy in triple negative breast cancer patients who do not achieve a pathological complete response, for which there are few detailed QOL analyses[9].

Here, we report the detailed TACT2 QOL sub-study, namely the co-primary outcome (psychological distress) and the secondary outcomes (impact on physical symptoms and functional domains). We analysed all questionnaire data and built a comprehensive picture of patient experiences during chemotherapy and in the following 24-months. Our hypotheses were: 1) the more intense regimens (aE and CMF) would result in worse patient-reported physical symptoms and worse impact on patient functioning at end of treatment period; 2) these differences would resolve by 12 and 24-months.

Methods

Study design and participants

The overall TACT2 study design has been described in detail elsewhere [7]. In brief, TACT2 was a multicentre, phase III, randomized, open label, parallel controlled trial of adjuvant non-taxane chemotherapy in women with early breast cancer with sequential E-CMF chemotherapy as control group. In a 2x2 factorial design patients were randomised in a 1:1:1:1 ratio to receive either standard E followed by CMF (E-CMF), accelerated E followed by CMF (aE-CMF), standard E followed by capecitabine (E-capecitabine) or aE followed by capecitabine (aE-capecitabine). Eligible patients were women or men aged 18 years or older with histologically confirmed invasive primary breast carcinoma (T0–3, N0–2, M0), who had undergone complete excision and were due to receive adjuvant chemotherapy. Patients had to be fit to receive any of the trial chemotherapy regimens; to have adequate bone marrow, hepatic, and renal function. Exclusion criteria included malignant disease in the previous 10 years, except ductal carcinoma in situ, basal- cell carcinoma, and cervical carcinoma in situ, locally advanced or distant disease, involved surgical margins and severe cardiac or renal disorders.

The trial was approved by the Scotland Multi-Research Ethics Committee (MREC 04/MRE00/88) and local research and development offices. Patients provided written informed consent before enrolment.

Randomisation and masking

Randomisation was performed via telephone to one of the four participating clinical trials units (Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, UK (ICR-CTSU), which had overall responsibility for trial coordination; Cancer Clinical Trials Unit, Scotland, Edinburgh, UK; Leeds Clinical Trials Research Unit, Leeds, UK; Cancer Research UK Clinical Trials Unit, Birmingham, UK). Computer-generated permuted blocks were used. Stratification was by centre, number of nodes involved (0 vs. 1-3 vs. ≥4), age (≤50 vs. >50) and endocrine treatment (planned vs. not planned).

Procedures

Treatments. Patients were randomised to receive either four cycles of E (100mg/m2) 3-weekly or aE (100m/m2 plus pegfilgrastim) 2-weekly; followed by four cycles of either CMF 4-weekly (600 mg/m2 cyclophosphamide intravenously days 1 and 8 or 100 mg/m2 orally days 1–14; 40 mg/m2 methotrexate intravenously days 1 and 8; 600 mg/m2 fluorouracil intravenously days 1 and 8) or Capecitabine 2500 mg/m2 14 days, 3-weekly. All patients were followed up at 12, 18, 24 months, then yearly for at least 10 years post-randomisation.

The Quality of Life (QOL)/toxicity sub-study was carried out in 44 of the 129 centres (Appendix 1), in which all patients were invited to complete QOL questionnaires with companion collection of detailed toxicity, reported by both clinicians and patients. The baseline questionnaires were completed in clinic after consent before randomization. Subsequent questionnaires were sent by post by the QOL sub-study coordinator (at Cancer Clinical Trials Unit, Edinburgh,UK). The timepoints for QOL questionnaires were selected to allow measurement immediately after E/aE and CMF/capecitabine (for acute effects), 12-month and 24-months post randomization (for late effects). In the first protocol version, the timing of assessments included a 6-week assessment during E/aE but this proved to be unfeasible in practice. The QOL data collection was temporarily suspended and the schedule was simplified (Protocol Version: 2, 1st September 2007). We refer to those two periods of QOL data collection as stages QL1 and QL2 (Appendix 2).

Outcomes

QOL was assessed using validated questionnaires.

Hospital Anxiety and Depression Scale (HADS) is a 14-item instrument with two sub-scales for anxiety and depression [10]. Scores range from 0 to 21 on each scale, higher scores indicating more distress. Scores ≥11 suggest probable cases of anxiety or depression, scores 8-10 indicate borderline cases. A combined score ≥19 is indicative of psychological distress.

EORTC QLQ-C30 (version 3·0) and breast module QLQ-BR23 (version 1·0). The QLQ-C30 measures health-related QOL of cancer patients in general, supplemented by cancer site-specific modules. QLQ-C30 has 30 questions addressing 5 functional scales (physical, role, social, emotional, cognitive), one Global Health Status/QOL scale, 3 symptom scales (fatigue, nausea/vomiting, pain), 5 symptom items (appetite loss, constipation, diarrhoea, dyspnoea, insomnia), one financial difficulties item [11]. The EORTC QLQ-BR23 focuses on breast cancer-specific issues, has 23 questions with 4 functional scales: body image, future perspective, sexual enjoyment,sexual functioning and 4 symptom scales: arm symptoms (swelling in arm or hand, arm or shoulder pain,difficulty raising the arm), breast/chest wall symptoms (pain, swelling, oversensitivity,skin problems in the area of the affected breast), systemic therapy side-effects (dry mouth, taste changes, sore eyes, hair loss, feeling ill, hot flashes, headaches, upset by hair loss) [12]. All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 are on a scale from 0 to 100, with missing items accounted for using published scoring guidelines [13]. Higher scores on the functional scales and GHS/QOL represent a superior level of functioning/better QOL, whereas higher scores in the symptom scales/items represent worse symptoms.

The protocol specified two co-primary QOL outcomes: Overall QOL (EORTC QLQ-C30 Global Health Status/QOL (GHQ/QOL) subscale) and HADS-Total score. GHS/QOL results have been published along with the patient-reported chemotherapy-specific toxicities during treatment [7] . Here we present the analysis of HADS and the pre-specified secondary QOL outcomes of interest: EORTC QLQ-C30 subscales **physical function, role function, fatigue and EORTC-BR23 subscales sexual function and systemic therapy side-effects** at the end of E/aE, end of CMF/capecitabine, 12 and 24-months. Exploratory analysis of the remaining subscales/items is included.

Statistical analysis

Sample size. The QOL sub-study aimed to include 1000 patients in order to provide complete case data on 800-850 patients, assuming 15-20% attrition at 12-months (based on TACT-trial). If there was a carry-over effect between the treatments, looking at 4 separate groups of 200-213 patients at 12-month assessment would provide 92%-94% power to detect a difference of ≥20% (from 40% to 60%) in any proportions (α=0.01). With no carry-over effect, combining treatment groups would provide 99% power for the same difference and significance level. Whilst for the main trial we did not expect an interaction between the two randomisations, we could not presume that for QOL so the QOL sub-study was powered for four-group comparison. For CMF-capecitabine comparison we had a-priori hypothesis expecting a better QOL in capecitabine arm, whereas for aE-E we didn't have a-priori hypothesis regarding QOL impact. Mean differences of ≥5 points at group level in scores between the E-CMF and experimental treatments were considered clinically relevant. A 5-point mean difference with standard deviation of 19 (TACT-trial) equates to a standardised difference of 0.27. The 800-850 patients in this comparison (400-425 in each group) would detect a standardised difference of ≥0.27 with ≥90% power (α=0.01).

QOL data at baseline and each timepoint (end of E/aE, end of CMF/capecitabine treatment, 12 and 24-months) were analysed descriptively using the subscale/item scores. Cross-sectional analysis of the differences between the two treatments (E vs aE; CMF vs capecitabine) used Mann-Whitney non-parametric tests. Analyses of QOL change scores (QOL score at each time point minus baseline score) were compared between groups using ANCOVA adjusting for baseline score. The mean change from baseline to each time point with 99% confidence intervals was plotted by treatment group.

Using FDA-recommended approach, known as responder analysis, we evaluated if the observed statistically significant differences in change scores on a treatment group level are clinically meaningful at the individual level [14]. Change scores were dichotomised according to whether an individual patient's QOL had deteriorated by at least 10 points or not (a 10-point change indicates a clinically meaningful difference in QLQ-C30 scores; for single symptom items this cut-off means a change of at least one response-category, i.e. from 'Not at all' to 'A little'). [15] We only looked at deterioration, as the clinical expectation in the adjuvant setting is that patients' symptoms and functioning get worse due to treatment toxicity, and improvements are not expected. Only available QoL data was analysed, without imputations or accounting for intercurrent events (as these were rare). The purpose of the responder analysis was descriptive, to aid interpretation of QoL changes for clinical audience and enable visual presentation of the multiple QoL domains by study arm.

Generalised estimating equations (GEE) models were used to analyse the data longitudinally across all timepoints, including covariates for randomized treatments E/aE and CMF/capecitabine, baseline score, time from baseline to follow-up questionnaire completion, QOL study stage (QL1 or QL2),age at randomisation and type of surgery (wide local excision or mastectomy). For each model, the following terms were included if found to improve the model fit: Interaction between randomised treatment group and timing of questionnaire (to account for possibility of treatment effects not being constant across time); Interaction between randomised phase 1 (E/aE) and phase 2 (CMF/capecitabine) treatments. An unstructured correlation matrix and robust standard errors were used for all models.

An exploratory subgroup analysis looking at patients' menopausal status at 18-months was performed for the pre-specified QoL subscales scores at 24-months. Three groups of patients were compared: premenopausal at baseline remaining premenopausal at 18-months (pre-pre), premenopausal at baseline and postmenopausal at 18-months (pre-post), and postmenopausal at baseline (post).

Statistical analysis was performed on intention-to-treat basis. All patients who completed their pre-randomisation questionnaire and at least one post-randomisaiton questionnaire. For all statistical comparisons, a significance level of 0.01 was used with associated 99% confidence intervals to make some allowance for multiple testing. Patient characteristics of those who did and did not complete a 24-month questionnaire were compared. No imputations for missing questionnaires were applied. A sensitivity analysis to assess the impact of the change of timings of assessments between the first (QL1) and second stage (QL2) of recruitment into the QOL sub-study was performed. Analyses of the change in QOL from baseline to end of phase 2 treatment were repeated separately for QL1 and QL2 patients for all QLQ-C30, QLQ-BR23 and HADS subscale scores.

Database snapshot was taken on 25th August 2015. All analyses were performed using STATA v13 or higher. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN68068041 and ClinicalTrials.gov, number NCT00301925.

Role of funding source
The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results
From Dec 16th, 2005-Dec 5th, 2008, 4391 patients (20 male) were randomised into the TACT2 trial, including 1281 (8 male)/1493 (85.8%) consecutive eligible patients from 44 centres which participated in the QOL-toxicity sub-study (Figure 1). Median follow-up was 85.6 month (IQR 80.6-95.9). Analysis was performed on complete QOL dataset (of Sept 15th, 2011) when all participants had passed 24-month timepoint. Pre-randomisation baseline questionnaires were completed by 1172/1281 (91%) and 1179/1281 (92%) completed at least one post-randomisation questionnaire. Compliance rates with questionnaire returns were between 73% and 83% during the treatment, and 53% and 66% at 12 and 24-months. Completion rates were similar across treatment groups except a lower compliance rate in E-CMF group at 12 and 24-months (Appendix 3). No differences were found by type of surgery and nodal status, but premenopausal patients were less likely to complete a 24-month questionnaire. Baseline QOL and HADS scores were similar for completers and non-completers.

Patients participating in the QOL sub-study were representative of the TACT2 population (Table 1). Data on race/ethnicity was not collected. The baseline questionnaires scores were similar between treatment groups (Table 2). Overall, 121/1119 (11%) had a combined HADS score indicative of psychological distress. Levels of functioning from EORTC measures were

generally good with the exception of sexual functioning. Insomnia and fatigue had the highest level of symptom reporting.

In the comparison of E vs aE (Table 3), HADS-Anxiety and HADS-Depression scores were similar between groups at the end of E/aE treatment (Appendix 4a). HADS change score analyses confirmed a similar pattern to cross-sectional analyses with no significant differences between E and aE (Figures 2a-b, Appendix 5a). HADS-Anxiety improved during the treatment and remained lower than baseline at 24-months, whereas HADS-Depression worsened during treatment followed by improvement at 12 and 24-months towards baseline levels.

EORTC QLQ-C30 subscales/items showed significantly worse physical and role function, fatigue and systemic side effects for aE compared with E, but no significant differences in sexual function (Table 3). Exploratory analysis of the remaining EORTC questionnaire scales/items suggested worse nausea/vomiting, appetite loss, constipation and social functioning for aE. Overall, 7 out of 14 EORTC-C30 scores were worse in aE group at the end of treatment, and 1 out of 8 EORTC-BR23 scores. The negative impact did not persist, with no significant difference between E and aE at the end of CMF/capecitabine nor at 12 or 24-months (Appendix 4b-e). Analysis of change scores showed similar results (Figures 2c-j, Appendix 5).

Responder analysis showed that 8% to 10% more patients receiving aE had clinically significant deterioration than those receiving E (Appendix 6a). None of these differences remained at end of CMF/capecitabine, 12 or 24-months (Appendix 6b).

The separate analysis of 577 patients who completed week 6 questionnaires in QL1 stage showed results consistent with the results described above, with aE significantly worse than E for nausea/vomiting, systemic side-effects, global QOL, role functioning in all analyses (data not shown).

In the comparison of CMF vs capecitabine (Table 3, Appendix 4a), no between group differences were seen at the end of CMF/capecitabine treatment in the cross-sectional analysis of HADS-Anxiety and HADS-Total score. HADS-Depression scores were significantly worse in CMF patients (p=0.0048). Change scores confirmed a similar pattern of no difference, except HADS-Total score: at the end of treatment CMF patients reported worse change scores (p=0.0093, Appendix 5a,b), with the difference persistent at 24-months (Figure 3a). This was due to worse HADS-Depression scores as HADS-Anxiety improved during the treatment.

Cross-sectional analysis of EORTC questionnaires showed that at the end of CMF/capecitabine treatment, patients on CMF reported significantly worse physical and sexual function, fatigue and systemic side-effects. No significant difference was seen for role function. Exploratory analysis of the remaining EORTC scales/items suggested worse dyspnoea, insomnia and constipation, social and cognitive function at the end of treatment. We explored if worse dyspnoea was related to anaemia: patients receiving CMF had more grade 1-2 anaemia (70/384,18%) that those on capecitabine (11/290,4%), but there was no association between anaemia severity and dyspnoea scores. Overall, 7 out of 14 EORTC

QLQ-C30 scores and 2 out of 8 QLQ-BR23 scores were worse in CMF group at the end of treatment. Persistently worse scores in patients receiving CMF were observed at 12-months (physical, role function, fatigue, systemic side effects, social function, insomnia) and 24-months (role functioning, fatigue, systemic side-effects, social function). (Appendix 4c-f). Analyses of change scores showed a similar pattern to cross-sectional analyses (Figure 3b-j; Appendix 5).

Responder analysis of individual patients at the end of CMF/capecitabine (Appendix 6c), showed larger proportions of patients had clinical deterioration in CMF group in physical function, fatigue, and systemic side effects but not role or sexual functioning. In the exploratory analysis, clinically meaningful deteriorations were seen in social function, dyspnoea, insomnia, constipation. Between 5% and 13% more patients receiving CMF had clinically meaningful deterioration than those receiving capecitabine. At 12-months clinically meaningful differences were found for physical functioning and insomnia. At 24-months differences were seen for fatigue and role function(Appendix 6d).

Longitudinal modelling of HADS scores did not show any statistically significant differences between E and aE, or between CMF and capecitabine Figure 4, Appendix 7). HADS-Depression and HADS-Total scores improved as time from baseline increased. Older age was associated with better scores for HADS-Anxiety and HADS-Total score. Patients who had mastectomy had higher HADS-Anxiety score than those with wide local excision.

The GEE models did not show any significant difference between E and aE for any QLQ-C30 or QLQ-BR23 subscales. CMF was significantly worse than capecitabine for physical and role function, fatigue and systemic side effects (Figure 4). In the exploratory analyses of the secondary outcomes, most subscale scores were worse for CMF: nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, social, cognitive functioning, and body image (Appendix 7). Except pain, breast/arm symptoms, all scores improved significantly as time from baseline increased. Associations between pain and type of hormonotherapy were explored, see below. Older age was associated with worse scores for physical functioning, sexual functioning, appetite loss and hair loss, but better scores for body image, future perspective, breast symptoms, emotional functioning, cognitive functioning and financial difficulty. Mastectomy was associated with worse EORTC emotional function than wide local excision, but there was no associations between the type of surgery and sexual function, body image, breast/arm symptoms. There was no significant difference between the two stages of QOL data collection.

To understand the persistent differences in functioning and symptoms at 24-months, we explored associations between menopausal status at 18-months and the pre-specified QOL subscales at 24-months. Change scores from baseline to 24-months were compared for three groups of patients: premenopausal at baseline remaining premenopausal at 18-months (pre-pre, n=154); premenopausal at baseline postmenopausal at 18-months (pre-post, n=228) and postmenopausal (n=489). Unadjusted analysis showed that patients whose menopausal status changed reported significantly worse scores on systemic side-effects subscale in comparison with the postmenopausal group or the group remaining premenopausal irrespective of treatment (mean change score 13.2, SD 12.16; 7.44, SD 12.19; 7.87, SD 13.26 respectively, $p<0.001$). Responder analysis showed that 50% of the

patients in the pre-post group had clinically meaningful deterioration in comparison with 28% in the other two groups. No differences were seen in physical, role, sexual function, fatigue, pain and HADS. Regression models adjusting for ER, PR status and planned endocrine treatment (4 categories: none, Tamoxifen, Tamoxifen followed by aromatase inhibitor, aromatase inhibitor) showed similar results (Appendix 8). Patients on any endocrine treatment reported worse physical function compared to those on none.

Discussion

Our results from pre-specified secondary QOL analysis confirmed the hypothesis that more intense chemotherapy (i.e. aE and CMF) led to more severe side-effects with worse impact on patient functioning. Patients treated with aE reported more problems in 9 out of 23 QOL scales (including Global Health/QOL reported previously). Fatigue, treatment side effects, physical, role and social functions were all worse at the end of treatment. To our knowledge, for the first time we demonstrated that this impact did not last and was not detectable 12-months after starting chemotherapy. CMF was associated with worse physical side effects than capecitabine and led to deterioration in physical, role and social functioning (10 of 23 QOL scales worse). These differences persisted at 12 and 24-months, contrary to our hypothesis of an expected recovery by 12-months. Responder analysis was implemented to understand if the differences were clinically significant. This showed that in the aE and CMF groups more patients had a clinically meaningful deterioration at the end of treatment compared to E and capecitabine respectively. Psychological distress measured by HADS, was different only in the CMF group where HADS-Depression was worse. This was not related to a change in menopausal status. Mastectomy was associated with higher anxiety and worse emotional function than wide local excision, but no impact on body image or sexual functioning was detected. The emotional impact may be related to the larger tumours at diagnosis, perceived risk and fear of recurrence, but this was not assessed in the trial.

Our findings that dose-dense (accelerated) epirubicin chemotherapy had more significant subjective toxicity and worse impact on patient functioning at the end of treatment are consistent with the QOL results from a tailored dose-dense chemotherapy trial comparing sequential dose-dense epirubicin-cyclophosphamide followed by docetaxel with standard chemotherapy (FEC-docetaxel) [16]. At the end of treatment, 13 of 15 symptoms and functions, measured by EORTC QLQ-C30, were worse in the dose-dense group. There was no long-term follow-up in the trial beyond treatment end. To our knowledge, we report the first long-term data showing that the increased subjective toxicity and functional limitations are temporary with recovery by 12-months.

This data is important to present and future patients and clinicians. The individual patient data meta-analysis (which included TACT2 results) confirmed a clinically significant 14% improvement in population outcomes from accelerated anthracycline therapy in early breast cancer, but there were limited QOL or toxicity data to help patients make an informed choice regarding cost-benefit balance between accelerated and standard chemotherapy [8]. The pivotal randomized trial of dose-dense chemotherapy (Intergroup Trial C9741/Cancer Leukemia Group B Trial 9741) evaluated toxicity in a subset of patients and did not include a QOL study [17]. The trial of FEC-docetaxel tailored dose-dense chemotherapy did not lead to better recurrence-free survival but resulted in increased

haematological toxicity and worse QOL during treatment [16]. Recent trial and accompanying editorial questions the value of anthracyclines as part of adjuvant treatment in HER-2 positive cancers [18]. Our robust QOL data, in almost 1000 patients (including 21% Her-2 positive cancers), provide an evidence-base for informing patients about the type and pattern of this additional toxicity, its impact on functioning and QOL during treatment and reassuringly its resolution after treatment.

Capecitabine is considered by practicing oncologists a well-tolerated chemotherapy with a manageable toxicity profile. Our comparison with CMF confirmed this impression. In a trial of older women (≥65 years), adjuvant chemotherapy with Capecitabine showed less physical symptoms, better functioning and QOL than standard adjuvant chemotherapy (CMF or anthracycline-containing), with the differences resolving by 12-months [19,20]. Our results of CMF vs capecitabine comparison in a younger population are consistent with the above, except the 12-months QOL recovery. The differences with the published data may be related to the younger patient population in our trial. We explored if this may be related to the higher amenorrhea rate in CMF vs capecitabine (75% vs 42%) but the only association was with systemic side-effects scale. One non-inferiority trial comparing classical CMF with another oral fluoropyrimidine (uracil-tegafur) showed similar efficacy but better QOL with oral chemotherapy, a finding consistent with out results[21].

Capecitabine is not currently recommended as a standard adjuvant treatment, but following CREATE-X trial it has become standard of care as adjuvant treatment in triple negative breast cancers with poor prognosis and residual disease, following neo-adjuvant anthracycline and/or taxane-containing chemotherapy [9]. ECOG-ACRIN EA1131 trial supported the use of capecitabine versus platinum in patients with residual triple-negative breast cancer after neoadjuvant chemotherapy [22]. The patient-reported outcomes data in EA1131 suggested worse side-effects with capecitabine than platinum at cycle 3, using a different QOL instrument (Functional Assessment of Cancer Therapy- Breast Cancer Simptom Index) and in a relatively small patient sample (n=331, n=296 completing QOL)[23]. However, the changes in QOL were small and resolved after treatment, similar to TACT2 results. The reassuring QOL results from our trial further support shared decision-making in this group of patients.

A strength of the TACT2 trial and its QOL sub-study is a large geographically wide UK sample. The QOL sub-study participating centres were not pre-selected and all patients from those centres were eligible thus reducing the risk of bias. The QOL subset was similar to the total TACT2 sample in baseline clinical and demographic characteristics. Providing detailed data on QOL impacts of 4 different adjuvant treatments, alongside examination of the clinical significance of the differences via responder analysis, is valuable and informative to both patients and clinicians in supporting shared decision-making.

Limitations to this study should be acknowledged. Patient consent rate (85.6%) and compliance with completion of QOL measures (92% provided at least one questionnaire after randomization) is consistent with other similar trials using postal questionnaires over long time-periods. Overview of 14 clinical trials showed compliance rates per study from 84.7% to 97.2% [24]. The compliance was high during the treatment period; it reduced to about 60% at 12 and 24-months. Exploration of patterns of missing data at 24-months

showed younger premenopausal patients were less compliant. Therefore the results at 24-months may not reflect their experiences. A weakness of the QOL sub-study design is the change of the data collection time-points during the study, dictated by pragmatism. The longitudinal modelling explored potential impact of the different scheduling and concluded that the results were not different. Another limitation of the QOL sub-study is the analysis of available data without imputations or accounting for intercurrent events. This choice was made as the number of intercurrent events was low, without differences between the trial arms and unlikely to influence the results.

Currently, there is a range of chemotherapy regimens for adjuvant breast cancer treatment. TACT2 trial showed that if taxanes are not indicated or contraindicated, treatment with epirubicin followed by capecitabine in 3-week cycles is effective and well-tolerated option. This detailed QOL analysis supports the main TACT2 trial conclusion. Whilst the TACT2 trial did not itself find a significant improvement for accelerated chemotherapy, the subsequent meta-analysis, found a reduction in breast cancer recurrences. Two-weekly adjuvant chemotherapy is now offered as standard of care in high-risk early breast cancer, but with few data to inform patients about the extent of associated toxicity and impacts on QOL. Our data rectify that information gap, giving patients and clinicians details on the additional symptom and QOL burden, and importantly confirm that this additional burden resolves within 1-year of starting therapy. The favourable QOL data on capecitabine supports its use as further 'rescue' adjuvant treatment after neo-adjuvant chemotherapy with residual disease in patients with triple-negative cancers.

Contributors

GV, PB-L, HE, AMB, PC, RC, AW, PE, RS ,JMB and DC were involved in the study design. DC oversaw the trial, GV oversaw the QOL sub-study. GV, PB-L, HE, DB, AMB, PC, RC, MV, AW, PE, RS were members of the trial management group. PC and GV did the literature searches. GV, JPM, JSH, CE did the data analysis, and GV, JPM, JSH, CE, DC, JMB interpreted the data. GV and JSH accessed and verified the data. GV, PB-L, HE, AMB, PC, RC, MV, AW, GB recruited patients. AMB and GB were principal investigator recruiter and involved with ongoing management decisions on publication, trial development, and manuscript review. GV, JSH, CE, DC and JMB wrote the paper. PB-L, HE, DB, AMB, PC, RC, MV, AW, GB, PE and RS reviewed the drafts. GV, DC and JMB gave final approval of the paper.

Declarations of interest

GV has received support for the present manuscript from the University of Leeds (payment for time working on manuscript), personal fees from Pfizer, Roche (none related to the manuscript) and was a member of the European Organisation for Research and Treatment of Cancer (EORTC) Board of directors (not related to this manuscript). **RC** has received personal fees from Sanofi, ACE Oncology, Amgen and Beigene, patents, planned, issued or pending with Inbiomotion, personal fee from AstraZeneca and stock options in Inbiomotion (biomarker in development). **MV** has received institutional grants from AstraZeneca, Genomic Health, Novartis, Pfizer, Roche, personal fees from Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Novartis, Pfizer, Roche, Seagen and received personal fees for advisory board work for AstraZeneca, Daiichi-Sankyo, Exact Sciences, Gilead, Lilly, Merck, Novartis, Pfizer, Roche and Seagen. **AW** has received National Institute for Health Research (NIHR) HTA and NIHR institutional grants. **RS**

has received a grant from NIHR (salary support). **JMB** has received support for the present manuscript from Cancer Research UK (research costs to the clinical trials offices), and educational grants funding from Roche, Amgen and Pfizer, institutional grants from AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology, Novartis (previously GSK), Eli Lilly, Janssen-Cilag and Clovis Oncology. **DC** has received personal fees from Aptitude Health, Pfizer, Celldex Therapeutics Inc, Carnall Farrar, Astrazeneca, Celgene Corporation, Eli Lilly, Roche, Novartis, Merck Sharp Dohme, PUMA Biotechnology, F. Hoffmann-La Roche AG, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Therapeutics, Genentech Inc, GSK (Glaxo SmithKline), ICON Clinical Research, Prima BioMED, RTI Health Solutions, Synthon Biopharmaceuticals BV : note name change to Byondis April 2020, Succinct Medical Communications, Seagen, SANOFI, Sapience Therapeutics Ltd, Bexon / Zymeworks Biopharmaceuticals Inc., NexGen, IQVIA: Institutional grants from Cancer Research UK, HTA, Breast International Group (BIG), Breast Cancer Institute, European Cancer Organisation. The other authors (JSS, CE, PBL, HE, GB, PE, DB, AMB, PC) declare no competing interests.

Acknowledgments

We thank the patients, their relatives and treating clinicians, and the hospitals who participated in this study. We wish to acknowledge especially the Cancer Clinical Trials Unit, Scotland, Edinburgh, UK for coordinating the collection of the QOL data. We thank Cancer Research UK for funding the study, Amgen, Pfizer, and Roche, for unrestricted educational grants, and the National Institute for Health Research cancer research networks in England and their equivalent NHS R&D-funded networks in Scotland, Wales, and Northern Ireland for “in-kind” support. We thank the members of the independent data monitoring committee and the Clinical Trials and Statistics Unit at the Institute of Cancer Research overarching trials steering committee, and the two co-sponsoring organisations, The Institute of Cancer Research and NHS Lothian. Roche supplied free capecitabine and Amgen provided subsidised pegfilgrastim for trial use.

References

1. Burstein HJ, Curigliano G, Thurlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol* 2021; **32**(10): 1216-35.
2. Hall E, Cameron D, Waters R, et al. Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing regimen and standard anthracycline based chemotherapy for early breast cancer: 6 year results from the UK TACT trial (CRUK/01/001). *Eur J Cancer* 2014; **50**(14): 2375-89.
3. Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer--taking stock. *J Natl Cancer Inst* 2003; **95**(4): 263-81.
4. Lemieux J, Goodwin PJ, Bordeleau LJ, Lauzier S, Theberge V. Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001-2009). *J Natl Cancer Inst* 2011; **103**(3): 178-231.
5. Del Mastro L, Costantini M, Morasso G, et al. Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. *Eur J Cancer* 2002; **38**(3): 359-66.
6. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med* 2006; **355**(18): 1851-62.
7. Cameron D, Morden JP, Canney P, et al. Accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer in the randomised UK TACT2 trial (CRUK/05/19): a multicentre, phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2017; **18**(7): 929-45.
8. Early Breast Cancer Trialists' Collaborative G. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet* 2019; **393**(10179): 1440-52.
9. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med* 2017; **376**(22): 2147-59.
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70.
11. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**(5): 365-76.
12. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996; **14**(10): 2756-68.
13. EORTC. EORTC QLQ-C30 Scoring Manual. 2001. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf (accessed 2nd April 2022 2022).
14. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11**(2): 163-9.
15. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**(1): 139-44.

16. Foukakis T, von Minckwitz G, Bengtsson NO, et al. Effect of Tailored Dose-Dense Chemotherapy vs Standard 3-Weekly Adjuvant Chemotherapy on Recurrence-Free Survival Among Women With High-Risk Early Breast Cancer: A Randomized Clinical Trial. *JAMA* 2016; **316**(18): 1888-96.
17. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; **21**(8): 1431-9.
18. Hurvitz SA. Anthracycline Use in ERBB2-Positive Breast Cancer: It Is Time to Re-TRAIN. *JAMA Oncol* 2021; **7**(7): 975-7.
19. Kornblith AB, Lan L, Archer L, et al. Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. *J Clin Oncol* 2011; **29**(8): 1022-8.
20. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009; **360**(20): 2055-65.
21. Watanabe T, Sano M, Takashima S, et al. Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as postoperative chemotherapy in patients with node-negative, high-risk breast cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. *J Clin Oncol* 2009; **27**(9): 1368-74.
22. Mayer IA, Zhao F, Arteaga CL, et al. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. *J Clin Oncol* 2021; **39**(23): 2539-51.
23. Smith KLZ, F.; Mayer,I.A.;Tevaarwerk,A.J.; Garcia,S.F.; Arteaga,C.L.; SymmansW.F.; Park,B.H.; Burnette,B.L.;Makower,D.F.;Block,M.;Morley,K.A.;Jani,C.R.; Mescher,C.;Dewani,S.J.;Brown-Glaberman,U.;Flaum,L.E.;Mayer,E.L.;Sikov,W.M.;Rodler,E.T.; DeMichele,A.M.;SparanoJ.A.;Wolff,A.C.;Miller,K.D.;Wagner,L.I. Abstract P4-10-02: Patient-reported outcomes in EA1131: A randomized phase III trial of platinum vs. capecitabine in patients with residual triple-negative breast cancer after neoadjuvant chemotherapy. *Cancer Research* 2022; **82**: P4-10-02.
24. Atherton PJ, Burger KN, Pederson LD, Kaggal S, Sloan JA. Patient-reported outcomes questionnaire compliance in Cancer Cooperative Group Trials (Alliance N0992). *Clin Trials* 2016; **13**(6): 612-20.

Quality of life results in the UK TACT2 Trial of accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer: a multicentre, phase 3, open-label, randomised, controlled trial (CRUK/05/19)

Galina Velikova, James P Morden*, Joanne S Haviland, Charlotte Emery, Peter Barrett-Lee, Helena Earl, David Bloomfield, Adrian Murray Brunt, Peter Canney 7, Robert Coleman, Mark Verrill, Andrew Wardley, Gianfilippo Bertelli, Paul Ellis, Rob Stein, Judith M Bliss, David Cameron on behalf of the TACT2 Trial Management Group

Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK (Prof G Velikova FRCP PhD)

Institute of Cancer Research Clinical Trials and Statistics Unit, Institute of Cancer Research, London, UK (J P Morden MSc, J S Haviland MSc, C Emery MSc, Prof J M Bliss MSc)

Department of Oncology, Velindre University NHS Trust, Cardiff, UK (Prof P Barrett-Lee MD)

Department of Oncology, University of Cambridge and NIHR Cambridge Biomedical Research Centre, UK (Prof H Earl PhD)

Department of Oncology, University Hospitals Sussex, Brighton, UK (Prof DJ Bloomfield FRCR, Prof G Bertelli PhD)

School of Medicine, University of Keele, Keele & Department of Oncology, University Hospitals of North Midlands, Stoke-on-Trent, UK (Prof A M Brunt FRCP)

Beatson Oncology Center, Glasgow, UK (P Canney MD)

Department of Oncology, Weston Park Hospital, Sheffield, UK (Prof R Coleman FRCP)

Department of Oncology, Northern Centre for Cancer Care, Freeman Hospital, Newcastle, UK (M Verrill FRCP)

Outreach Research & Innovation Group, Manchester, UK (Prof A Wardley MD)

King's College London and Leaders in Oncology Care (LOC) London, UK (Prof P Ellis FRCP)

University College London Hospitals, London, UK (Prof R Stein FRCP)

University of Edinburgh Cancer Centre, Institute of Genetics and Cancer, Western General Hospital, Edinburgh, UK (Prof D Cameron MD)

*deceased

Correspondence to:
Prof Galina Velikova
Leeds Institute of Medical Research at St James's, University of Leeds
Leeds Cancer Centre, St James's University Hospital, Bexley wing
Beckett street
Leeds, LS9 7TF, UK
g.velikova@leeds.ac.uk

Summary~~Abstract~~

Background:
Adjuvant chemotherapy for early breast cancer (EBC) improves outcomes but its toxicity impacts patients' quality of life (QOL). ~~The~~ UK TACT2 trial investigated whether accelerated epirubicin (aE) improves time-to-recurrence (TTR) and if oral capecitabine is non-inferior to cyclophosphamide, methotrexate and fluorouracil (CMF) for efficacy with less toxicity. Results showed no aE benefit and capecitabine was non-inferior. As part of the QOL sub-study we report here the impact of chemotherapies on psychological distress, physical symptoms and functional domains.

Methods: ~~From Dec 16th, 2005-Dec 5th, 2008, 4391 EBC patients were randomised 2x2 between E-CMF, aE-CMF, E-capecitabine or aE-capecitabine.~~
TACT2 was multicentre, phase 3, randomised, controlled trial, which enrolled patients aged ≥18 years from 129 UK centres with histologically confirmed node-positive or high-risk node-negative operable breast cancer, following complete excision, and due to receive adjuvant chemotherapy. Patients were randomised to four cycles of 100 mg/m2 epirubicin either every 3 weeks (standard epirubicin) or every 2 weeks with 6 mg pegfilgrastim on day 2 of each cycle (accelerated epirubicin), followed by four 4-week cycles of either classic cyclophosphamide, methotrexate, and fluorouracil (CMF; 600 mg/m2 cyclophosphamide intravenously on days 1 and 8 or 100 mg/m2 orally on days 1–14; 40 mg/m2 methotrexate intravenously on days 1 and 8; and 600 mg/m2 fluorouracil intravenously on days 1 and 8 of each cycle) or four 3-week cycles of 2500 mg/m2 capecitabine (1250 mg/m2 given twice daily on days 1–14 of each cycle).
The randomisation schedule was computer generated in random permuted blocks, stratified by centre, number of nodes involved (none vs 1-3 vs ≥4), age (≤50 vs >50 years), and planned endocrine treatment (yes/no). The primary endpoint was TTR which has been reported. QOL was one of the secondary outcomes. All patients from a subset of 44 centres were invited to complete QOL questionnaires (Hospital Anxiety Depression Scale, EORTC QLQ-C30, EORTC QLQ-BR23) at baseline, end aE/E, end CMF/capecitabine, 12 and 24-months post-randomisation. QOL substudy pre-specified two co-primary QOL outcomes: Overall QOL (already reported) and HADS-Total score. Pre-specified secondary QOL outcomes were EORTC QLQ-C30 subscales physical function, role function, fatigue and EORTC-BR23 subscales sexual function and systemic therapy side-effects. QOL sub-study needed 1000 patients to provide complete case data on 800-850 patients at 12-months (assuming 15-20% attrition) and allow analysis of 4 separate groups of 200-213 patients with 92%-94% power to detect a difference of >20% in any proportions (α=0.01). Intention-to-treat analysis included cross-sectional comparisons (Mann-Whitney non-parametric tests), change scores comparsions (ANCOVA adjusting for baseline score) and generalised estimating equations models. This trial is registered with ISRCTN, number 68068041, and with ClinicalTrials.gov, number NCT00301925.

~~Patients from a subset of 44/129 centres completed QOL questionnaires (Hospital Anxiety Depression Scale (HADS,co-primary endpoint), EORTC QLQ-C30, EORTC QLQ-BR23) at baseline, end aE/E, end CMF/capecitabine, 12 and 24-months post-randomisation. Data were analysed by cross-sectional comparisons and generalised estimating equations models.~~

Findings: From Dec 16th, 2005-Dec 5th, 2008, 4391 patients (20 male) were randomised in TACT2 trial, 1281(86%, 8 male) patients of 1493 approached consented to the QOL sub-study. Median follow-up 85.6 month (IQR 80.6-95.9). ~~;~~ Analysis was performed on complete QOL dataset (of Sept 15th, 2011) when all participants had passed 24-month timepoint. Pre-randomisation questionnaires were completed by 1172/1281 (91%) patients, 1179/1281 (92%) completed at least one post-randomisation questionnaire. ~~-~~For HADS (co-primary QOL outcome, t~~T~~he only differences ~~in HADS~~ were ~~worse~~ end-of-treatment scores worse for CMF vs capecitabine: HADS-Depression ~~for CMF~~(p=0.0048) and HADS-Total change score (p=0.0093). aE led to worse physical (p=0.0065), role function (p<0.0001) (but not sexual function, p=0.36), fatigue (0.00018), systemic side effects (0.00012) compared with E during treatment, but the impact did not persist.~~-. CMF caused~~ W~~worse physical symptoms than capecitabine and deterioration in physical, role and social functioning~~ Worse physical (0.0048) and sexual function (0.0053), fatigue (<0.0001) and systemic side-effects (<0.0001) were seen for CMF vs capcitabine end-of-tretament, ~~(9/23 QOL scales worse),~~. T~~-t~~hese differences persisted at 12 and 24-months.

Interpretation: aE was associated with worse QOL compared with E but only during treatment. These findings will help patients/clinicians make an informed choice about accelerated chemotherapy. CMF had worse QOL effects than capecitabine, persistent for 24-months. The favourable capecitabine QOL compared with CMF supports its use as an adjuvant option post-neoadjuvant chemotherapy in patients with triple-negative breast cancer.

~~This trial is registered as ISRCTN68068041, ClinicalTrials.gov NCT00301925.~~
Funding. Cancer Research UK, Amgen, Pfizer, and Roche.

Research in context

Evidence before this study

At the time this study was designed in 2004, the optimal adjuvant chemotherapy treatment for early breast cancer had not been established. Some trials showed improved efficacy with ~~shortening the interval between chemotherapy cycles by using growth factors to speed recovery of peripheral neutrophils. This approach was called~~ accelerated or dose-dense chemotherapy (shorter intervals between chemotherapy cycles by using growth factor). This approach ~~and~~ was becoming the standard of care in parts of the world, without robust data on the impact of the accelerated treatment on patients' quality of life (QOL). At the time, one of the standard UK regimens for moderate risk early breast cancer was epirubicin (E) followed by cyclophosphamide, methotrexate, and fluorouracil (CMF). The toxicity of this treatment was a concern, with observations from two other trials ~~that~~ of treatment-related deaths ~~occurred while patients were~~during ~~taking~~ CMF. TACT2 trial was designed to investigate whether use of accelerated E (aE) would improve time to tumour recurrence and whether using oral capecitabine instead of CMF would be non-inferior for efficacy but better tolerated in terms of toxicity and impact on QOL.

In 2003, a systematic review of health-related quality of life measuremen in breast cancer (Goodwin P et al, 2003) identified only 6 randomised controlled trials of adjuvant chemotherapy in breast cancer with QOL results, suggesting a transient negative impact, especially of more aggressive treatments (anthracyclines, taxanes). An update of this systematic review in 2011 (Lemieux J et al, 2011 JNCI) , reported further 16 trials comparing different chemotherapy treatments, confirming a decline in QOL during treatment with recovery by 12 months. There was only one trial of dose-dense chemotherapy (Del Mastro et al, 2002) which showed worse psychological distress during dose-dense treatment with recovery by 6 months. One non-inferiority trial comparing classical CMF with an oral fluoropyrimidine (uracil-tegafur) showed similar efficacy but better QOL with oral chemotherapy (Watanabe t et al, 2009).

Formatted: Space Before: 12 pt

TACT2 trial primary outcome showed no benefit for aE and confirmed non-inferiority of capecitabine over CMF in time to tumour recurrence. The results confirmed better tolerability of capecitabine over CMF (with standard toxicity reporting by clinicians), with worse overall quality of life (primary QOL outcome) reported by patients on CMF at the end of treatment and up to 24-months. aE led to worse overall ~~quality of life~~QOL during the treatment, which was not sustained by the end of chemotherapy.

In 2019, an individual patient-level meta-analysis of dose-dense chemotherapy (which included TACT2 data) found modest benefits of 13% reduction in mortality and 14% reduction in cancer recurrences for accelerated chemotherapy. However, the long-term ~~quality of life~~QOL effects of the dose-dense chemotherapy are less well known. Only one trial of dose-dense chemotherapy included QOL measures, reporting worse QOL impact during and at end-of-treatment but did not evaluate QOL in the longer term (Foukakis T et al 2016). ~~, highlighting the need for patient-reported data to inform clinician-patient communication and shared decisions making.~~

Here, we report the detailed TACT2 quality of life sub-study, including analysis of physical symptoms and functional impact, to build a comprehensive picture of patient experiences during adjuvant chemotherapy and in the following 24-months.

Formatted: Font color: Auto

Added value of this study

This study confirmed the negative impact of accelerated chemotherapy ~~aE~~ during the treatment with adiditonal information of the range of affected QOL areas (physical and role functions, fatigue and self-reported side-effects). ~~led to significant negative impact on patients' physical symptoms and functioning during the treatment, but this was short-lived. Fatigue, treatment side effects, physical, role and social functions were all worse at the end of treatment.~~ To the best of our knowledge, ~~F~~for the first time we demonstrated that this impact did not last and was no longer detectable 12-months after starting chemotherapy. CMF was associated with worse physical side effects, than capecitabine and led to worse physical, role and social functioning. Importantly, we showed that these differences persisted up to 24-months.

Implications of all the available evidence

The meta-analysis of adjuvant dose-dense chemotherapy established this approach as a standard of care. Our detailed ~~quality of life~~QOL analysis provides patients and clinicians with details on the range and extent of the additional symptom burden and ~~quality of life~~QOL impact, and importantly confirm that this additional burden resolves within 12-months of starting therapy. ~~These findings on the long-term quality of life effects may have broader relevance to other accelerated chemotherapy regimens.~~

The lasting side-effects and functional impact of CMF adds to the clinical reasons for further reducing its use as part of adjuvant treatments for early breast cancer. The favourable symptom burden and ~~quality of life~~functions data on capecitabine supports its increased use as 'rescue' adjuvant treatment after neo-adjuvant chemotherapy with residual disease in triple negative patients.

Introduction

Improvements in outcomes for women diagnosed with early breast cancer led to an increased emphasis on evaluating toxicity of the adjuvant chemotherapy regimens and the longer-term impact on patients' health-related quality of life (QOL). This approach is especially important when more intensive treatments result in small survival gains. Even in the era of genomic testing [1], oncologists must balance toxicity and estimated benefits to help patients decide about adjuvant chemotherapy when the majority of patients would not individually benefit. For example, QOL results from the TACT trial showed that taxane-containing chemotherapy impaired global QOL and affected more QOL domains during treatment than anthracycline-based chemotherapy. However, most QOL parameters returned to baseline 2-years post-treatment[2]. The patient-reported data is acknowledged to plays a key role in shared decision-making about adjuvant chemotherapy.

In 2003, a systematic review of health-related quality of life measuremen in breast cancer identified only 6 randomised controlled trials of adjuvant chemotherapy in breast cancer with QOL results, suggesting a transient negative impact, especially of more aggressive treatments (anthracyclines, taxanes)[3]. An update of this systematic review in 2011[4], reported further 16 trials comparing different chemotherapy treatments, confirming a decline in QOL during treatment with recovery by 12 months. However, there was only one reported trial of dose-dense chemotherapy with QOL measurement which showed worse psychological distress during dose-dense treatment with recovery by 6 months[5].

TACT2 was a multicentre, phase III, randomised controlled trial of adjuvant non-taxane chemotherapy in women with early breast cancer, using 2x2 factorial design. The control group was sequential epirubicin(E)-CMF chemotherapy (based on NEAT trial results)[6]. Two hypotheses were tested: 1) accelerating epirubicin (aE) gives superior benefits in time to tumour recurrence and 2) using oral capecitabine instead of CMF would be non-inferior for patient outcomes but advantageous with less toxicity and better QOL. Primary outcome results showed no benefit for aE and confirmed non-inferiority of capecitabine to CMF in time to tumour recurrence[7]. Only the primary QOL outcome (Global Health Status/QOL) was reported in the main publication. The results confirmed better tolerability of capecitabine over CMF, with worse global QOL observed in patients on CMF at treatment end, and importantly, the difference persisting at 12 and 24-months, suggesting long-term negative effects of CMF. In the E vs aE comparison, Global Health Status/QOL was worse in aE during the treatment, but did not persist afterwards. We now report the impact of the treatments on a wider range of patient symptoms and experiences (psychological distress, physical, role and social functioning) to understand the reasons for the global QOL differences and to provide detailed information to future patients. This research question is important and relevant to current clinical practice, as the meta-analysis of dose-dense chemotherapy found only modest benefits (13% mortality reduction; 14% reduction in cancer recurrences). However, the short and long-term QoL effects of dose-dense chemotherapy are less well known, highlighting the need for patient-reported data to inform clinician-patient communication and shared decisions-making [8]. Furthermore, current practice includes the use of capecitabine post-neoadjuvant chemotherapy in triple negative breast cancer patients who do not achieve a pathological complete response, for which there are few detailed QOL analyses[9].

Here, we report the detailed TACT2 QOL sub-study, namely the co-primary outcome (psychological distress) and the secondary outcomes (impact on physical symptoms and functional domains). We analysed all questionnaire data and built a comprehensive picture of patient experiences during chemotherapy and in the following 24-months. Our hypotheses were: 1) the more intense regimens (aE and CMF) would result in worse patient-reported physical symptoms and worse impact on patient functioning at end of treatment period; 2) these differences would resolve by 12 and 24-months.

Methods

Study design and participants

The overall TACT2 study design has been described in detail elsewhere [7]. In brief, TACT2 was a multicentre, phase III, randomized, open label, parallel controlled trial of adjuvant non-taxane chemotherapy in women with early breast cancer with sequential E-CMF chemotherapy as control group. In a 2x2 factorial design patients were randomised in a 1:1:1:1 ratio to receive either standard E followed by CMF (E-CMF), accelerated E followed by CMF (aE-CMF), standard E followed by capecitabine (E-capecitabine) or aE followed by capecitabine (aE-capecitabine). Eligible patients were women or men aged 18 years or older with histologically confirmed invasive primary breast carcinoma (T0–3, N0–2, M0), who had undergone complete excision and were due to receive adjuvant chemotherapy. Patients had to be fit to receive any of the trial chemotherapy regimens; to have adequate bone marrow, hepatic, and renal function. Exclusion criteria included malignant disease in the previous 10 years, except ductal carcinoma in situ, basal- cell carcinoma, and cervical carcinoma in situ, locally advanced or distant disease, involved surgical margins and severe cardiac or renal disorders.

The trial was approved by the Scotland Multi-Research Ethics Committee (MREC 04/MRE00/88) and local research and development offices. Patients provided written informed consent before enrolment.

Randomisation and masking

Randomisation was performed via telephone to one of the four participating clinical trials units (Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, UK (ICR-CTSU), which had overall responsibility for trial coordination; Cancer Clinical Trials Unit, Scotland, Edinburgh, UK; Leeds Clinical Trials Research Unit, Leeds, UK; Cancer Research UK Clinical Trials Unit, Birmingham, UK). Computer-generated permuted blocks were used. Stratification was by centre, number of nodes involved (0 vs. 1-3 vs. ≥4), age (≤50 vs. >50) and endocrine treatment (planned vs. not planned).

Procedures

Treatments. Patients were randomised to receive either four cycles of E (100mg/m2) 3-weekly or aE (100m/m2 plus pegfilgrastim) 2-weekly; followed by four cycles of either CMF 4-weekly (600 mg/m2 cyclophosphamide intravenously days 1 and 8 or 100 mg/m2 orally days 1–14; 40 mg/m2 methotrexate intravenously days 1 and 8; 600 mg/m2 fluorouracil intravenously days 1 and 8) or Capecitabine 2500 mg/m2 14 days, 3-weekly. All patients were followed up at 12, 18, 24 months, then yearly for at least 10 years post-randomisation.

The Quality of Life (QOL)/toxicity sub-study was carried out in 44 of the 129 centres (Appendix 1), in which all patients were invited to complete QOL questionnaires with companion collection of detailed toxicity, reported by both clinicians and patients. The baseline questionnaires were completed in clinic after consent before randomization. Subsequent questionnaires were sent by post by the QOL sub-study coordinator (at Cancer Clinical Trials Unit, Edinburgh,UK). The timepoints for QOL questionnaires were selected to allow measurement immediately after E/aE and CMF/capecitabine (for acute effects), 12-month and 24-months post randomization (for late effects). In the first protocol version, the timing of assessments included a 6-week assessment during E/aE but this proved to be unfeasible in practice. The QOL data collection was temporarily suspended and the schedule was simplified (Protocol Version: 2, 1st September 2007). We refer to those two periods of QOL data collection as stages QL1 and QL2 (Appendix 2).

Outcomes

QOL was assessed using validated questionnaires.

Hospital Anxiety and Depression Scale (HADS) is a 14-item instrument with two sub-scales for anxiety and depression [10]. Scores range from 0 to 21 on each scale, higher scores indicating more distress. Scores ≥11 suggest probable cases of anxiety or depression, scores 8-10 indicate borderline cases. A combined score ≥19 is indicative of psychological distress.

EORTC QLQ-C30 (version 3·0) and breast module QLQ-BR23 (version 1·0). The QLQ-C30 measures health-related QOL of cancer patients in general, supplemented by cancer site-specific modules. QLQ-C30 has 30 questions addressing 5 functional scales (physical, role, social, emotional, cognitive), one Global Health Status/QOL scale, 3 symptom scales (fatigue, nausea/vomiting, pain), 5 symptom items (appetite loss, constipation, diarrhoea, dyspnoea, insomnia), one financial difficulties item [11]. The EORTC QLQ-BR23 focuses on breast cancer-specific issues, has 23 questions with 4 functional scales: body image, future perspective, sexual enjoyment,sexual functioning and 4 symptom scales: arm symptoms (swelling in arm or hand, arm or shoulder pain,difficulty raising the arm), breast/chest wall symptoms (pain, swelling, oversensitivity,skin problems in the area of the affected breast), systemic therapy side-effects (dry mouth, taste changes, sore eyes, hair loss, feeling ill, hot flashes, headaches, upset by hair loss) [12]. All scores for the EORTC QLQ-C30 and EORTC QLQ-BR23 are on a scale from 0 to 100, with missing items accounted for using published scoring guidelines [13]. Higher scores on the functional scales and GHS/QOL represent a superior level of functioning/better QOL, whereas higher scores in the symptom scales/items represent worse symptoms.

The protocol specified two co-primary QOL outcomes: Overall QOL (EORTC QLQ-C30 Global Health Status/QOL (GHQ/QOL) subscale) and HADS-Total score. GHS/QOL results have been published along with the patient-reported chemotherapy-specific toxicities during treatment [7] . Here we present the analysis of HADS and the pre-specified secondary QOL outcomes of interest: EORTC QLQ-C30 subscales **physical function, role function, fatigue and EORTC-BR23 subscales sexual function and systemic therapy side-effects** at the end of E/aE, end of CMF/capecitabine, 12 and 24-months. Exploratory analysis of the remaining subscales/items is included.

Statistical analysis

Sample size. The QOL sub-study aimed to include 1000 patients in order to provide complete case data on 800-850 patients, assuming 15-20% attrition at 12-months (based on TACT-trial). If there was a carry-over effect between the treatments, looking at 4 separate groups of 200-213 patients at 12-month assessment would provide 92%-94% power to detect a difference of ≥20% (from 40% to 60%) in any proportions (α=0.01). With no carry-over effect, combining treatment groups would provide 99% power for the same difference and significance level. Whilst for the main trial we did not expect an interaction between the two randomisations, we could not presume that for QOL so the QOL sub-study was powered for four-group comparison. For CMF-capecitabine comparison we had a-priori hypothesis expecting a better QOL in capecitabine arm, whereas for aE-E we didn't have a-priori hypothesis regarding QOL impact. Mean differences of ≥5 points at group level in scores between the E-CMF and experimental treatments were considered clinically relevant. A 5-point mean difference with standard deviation of 19 (TACT-trial) equates to a standardised difference of 0.27. The 800-850 patients in this comparison (400-425 in each group) would detect a standardised difference of ≥0.27 with ≥90% power (α=0.01).

QOL data at baseline and each timepoint (end of E/aE, end of CMF/capecitabine treatment, 12 and 24-months) were analysed descriptively using the subscale/item scores. Cross-sectional analysis of the differences between the two treatments (E vs aE; CMF vs capecitabine) used Mann-Whitney non-parametric tests. Analyses of QOL change scores (QOL score at each time point minus baseline score) were compared between groups using ANCOVA adjusting for baseline score. The mean change from baseline to each time point with 99% confidence intervals was plotted by treatment group.

Using FDA-recommended approach, known as responder analysis, we evaluated if the observed statistically significant differences in change scores on a treatment group level are clinically meaningful at the individual level [14]. Change scores were dichotomised according to whether an individual patient's QOL had deteriorated by at least 10 points or not (a 10-point change indicates a clinically meaningful difference in QLQ-C30 scores; for single symptom items this cut-off means a change of at least one response-category, i.e. from 'Not at all' to 'A little'). [15] We only looked at deterioration, as the clinical expectation in the adjuvant setting is that patients' symptoms and functioning get worse due to treatment toxicity, and improvements are not expected. Only available QoL data was analysed, without imputations or accounting for intercurrent events (as these were rare). The purpose of the responder analysis was descriptive, to aid interpretation of QoL changes for clinical audience and enable visual presentation of the multiple QoL domains by study arm.

Generalised estimating equations (GEE) models were used to analyse the data longitudinally across all timepoints, including covariates for randomized treatments E/aE and CMF/capecitabine, baseline score, time from baseline to follow-up questionnaire completion, QOL study stage (QL1 or QL2),age at randomisation and type of surgery (wide local excision or mastectomy). For each model, the following terms were included if found to improve the model fit: Interaction between randomised treatment group and timing of questionnaire (to account for possibility of treatment effects not being constant across time); Interaction between randomised phase 1 (E/aE) and phase 2 (CMF/capecitabine) treatments. An unstructured correlation matrix and robust standard errors were used for all models.

An exploratory subgroup analysis looking at patients' menopausal status at 18-months was performed for the pre-specified QoL subscales scores at 24-months. Three groups of patients were compared: premenopausal at baseline remaining premenopausal at 18-months (pre-pre), premenopausal at baseline and postmenopausal at 18-months (pre-post), and postmenopausal at baseline (post).

Statistical analysis was performed on intention-to-treat basis. All patients who completed their pre-randomisation questionnaire and at least one post-randomisaiton questionnaire. For all statistical comparisons, a significance level of 0.01 was used with associated 99% confidence intervals to make some allowance for multiple testing. Patient characteristics of those who did and did not complete a 24-month questionnaire were compared. No imputations for missing questionnaires were applied. A sensitivity analysis to assess the impact of the change of timings of assessments between the first (QL1) and second stage (QL2) of recruitment into the QOL sub-study was performed. Analyses of the change in QOL from baseline to end of phase 2 treatment were repeated separately for QL1 and QL2 patients for all QLQ-C30, QLQ-BR23 and HADS subscale scores.

Formatted: Font: (Default) Calibri, 12 pt

Database snapshot was taken on 25th August 2015. All analyses were performed using STATA v13 or higher. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN68068041 and ClinicalTrials.gov, number NCT00301925.

Role of funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From Dec 16th, 2005-Dec 5th, 2008, 4391 patients (20 male) were randomised into the TACT2 trial, including 1281 (8 male)/1493 (85.8%) consecutive eligible patients from 44 centres which participated in the QOL-toxicity sub-study (Figure 1). Median follow-up was 85.6 month (IQR 80.6-95.9). Analysis was performed on complete QOL dataset (of Sept 15th, 2011) when all participants had passed 24-month timepoint. Pre-randomisation baseline questionnaires were completed by 1172/1281 (91%) and 1179/1281 (92%) completed at least one post-randomisation questionnaire. Compliance rates with questionnaire returns were between 73% and 83% during the treatment, and 53% and 66% at 12 and 24-months. Completion rates were similar across treatment groups except a lower compliance rate in E-CMF group at 12 and 24-months (Appendix 3). No differences were found by type of surgery and nodal status, but premenopausal patients were less likely to complete a 24-month questionnaire. Baseline QOL and HADS scores were similar for completers and non-completers.

Patients participating in the QOL sub-study were representative of the TACT2 population (Table 1). Data on race/ethnicity was not collected. The baseline questionnaires scores were similar between treatment groups (Table 2). Overall, 121/1119 (11%) had a combined HADS score indicative of psychological distress. Levels of functioning from EORTC measures were

generally good with the exception of sexual functioning. Insomnia and fatigue had the highest level of symptom reporting.

In the comparison of E vs aE (Table 3), HADS-Anxiety and HADS-Depression scores were similar between groups at the end of E/aE treatment (Appendix 4a). HADS change score analyses confirmed a similar pattern to cross-sectional analyses with no significant differences between E and aE (Figures 2a-b, Appendix 5a). HADS-Anxiety improved during the treatment and remained lower than baseline at 24-months, whereas HADS-Depression worsened during treatment followed by improvement at 12 and 24-months towards baseline levels.

EORTC QLQ-C30 subscales/items showed significantly worse physical and role function, fatigue and systemic side effects for aE compared with E, but no significant differences in sexual function (Table 3). Exploratory analysis of the remaining EORTC questionnaire scales/items suggested worse nausea/vomiting, appetite loss, constipation and social functioning for aE. Overall, 7 out of 14 EORTC-C30 scores were worse in aE group at the end of treatment, and 1 out of 8 EORTC-BR23 scores. The negative impact did not persist, with no significant difference between E and aE at the end of CMF/capecitabine nor at 12 or 24-months (Appendix 4b-e). Analysis of change scores showed similar results (Figures 2c-j, Appendix 5).

Responder analysis showed that 8% to 10% more patients receiving aE had clinically significant deterioration than those receiving E (Appendix 6a). None of these differences remained at end of CMF/capecitabine, 12 or 24-months (Appendix 6b).

The separate analysis of 577 patients who completed week 6 questionnaires in QL1 stage showed results consistent with the results described above, with aE significantly worse than E for nausea/vomiting, systemic side-effects, global QOL, role functioning in all analyses (data not shown).

In the comparison of CMF vs capecitabine (Table 3, Appendix 4a), no between group differences were seen at the end of CMF/capecitabine treatment in the cross-sectional analysis of HADS-Anxiety and HADS-Total score. HADS-Depression scores were significantly worse in CMF patients (p=0.0048). Change scores confirmed a similar pattern of no difference, except HADS-Total score: at the end of treatment CMF patients reported worse change scores (p=0.0093, Appendix 5a,b), with the difference persistent at 24-months (Figure 3a). This was due to worse HADS-Depression scores as HADS-Anxiety improved during the treatment.

Cross-sectional analysis of EORTC questionnaires showed that at the end of CMF/capecitabine treatment, patients on CMF reported significantly worse physical and sexual function, fatigue and systemic side-effects. No significant difference was seen for role function. Exploratory analysis of the remaining EORTC scales/items suggested worse dyspnoea, insomnia and constipation, social and cognitive function at the end of treatment. We explored if worse dyspnoea was related to anaemia: patients receiving CMF had more grade 1-2 anaemia (70/384,18%) that those on capecitabine (11/290,4%), but there was no association between anaemia severity and dyspnoea scores. Overall, 7 out of 14 EORTC

QLQ-C30 scores and 2 out of 8 QLQ-BR23 scores were worse in CMF group at the end of treatment. Persistently worse scores in patients receiving CMF were observed at 12-months (physical, role function, fatigue, systemic side effects, social function, insomnia) and 24-months (role functioning, fatigue, systemic side-effects, social function). (Appendix 4c-f). Analyses of change scores showed a similar pattern to cross-sectional analyses (Figure 3b-j; Appendix 5).

Responder analysis of individual patients at the end of CMF/capecitabine (Appendix 6c), showed larger proportions of patients had clinical deterioration in CMF group in physical function, fatigue, and systemic side effects but not role or sexual functioning. In the exploratory analysis, clinically meaningful deteriorations were seen in social function, dyspnoea, insomnia, constipation. Between 5% and 13% more patients receiving CMF had clinically meaningful deterioration than those receiving capecitabine. At 12-months clinically meaningful differences were found for physical functioning and insomnia. At 24-months differences were seen for fatigue and role function(Appendix 6d).

Longitudinal modelling of HADS scores did not show any statistically significant differences between E and aE, or between CMF and capecitabine Figure 4, Appendix 7). HADS-Depression and HADS-Total scores improved as time from baseline increased. Older age was associated with better scores for HADS-Anxiety and HADS-Total score. Patients who had mastectomy had higher HADS-Anxiety score than those with wide local excision.

The GEE models did not show any significant difference between E and aE for any QLQ-C30 or QLQ-BR23 subscales. CMF was significantly worse than capecitabine for physical and role function, fatigue and systemic side effects (Figure 4). In the exploratory analyses of the secondary outcomes, most subscale scores were worse for CMF: nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, social, cognitive functioning, and body image (Appendix 7). Except pain, breast/arm symptoms, all scores improved significantly as time from baseline increased. Associations between pain and type of hormonotherapy were explored, see below. Older age was associated with worse scores for physical functioning, sexual functioning, appetite loss and hair loss, but better scores for body image, future perspective, breast symptoms, emotional functioning, cognitive functioning and financial difficulty. Mastectomy was associated with worse EORTC emotional function than wide local excision, but there was no associations between the type of surgery and sexual function, body image, breast/arm symptoms. There was no significant difference between the two stages of QOL data collection.

To understand the persistent differences in functioning and symptoms at 24-months, we explored associations between menopausal status at 18-months and the pre-specified QOL subscales at 24-months. Change scores from baseline to 24-months were compared for three groups of patients: premenopausal at baseline remaining premenopausal at 18-months (pre-pre, n=154); premenopausal at baseline postmenopausal at 18-months (pre-post, n=228) and postmenopausal (n=489). Unadjusted analysis showed that patients whose menopausal status changed reported significantly worse scores on systemic side-effects subscale in comparison with the postmenopausal group or the group remaining premenopausal irrespective of treatment (mean change score 13.2, SD 12.16; 7.44, SD 12.19; 7.87, SD 13.26 respectively, $p<0.001$). Responder analysis showed that 50% of the

patients in the pre-post group had clinically meaningful deterioration in comparison with 28% in the other two groups. No differences were seen in physical, role, sexual function, fatigue, pain and HADS. Regression models adjusting for ER, PR status and planned endocrine treatment (4 categories: none, Tamoxifen, Tamoxifen followed by aromatase inhibitor, aromatase inhibitor) showed similar results (Appendix 8). Patients on any endocrine treatment reported worse physical function compared to those on none.

Discussion

Our results from pre-specified secondary QOL analysis confirmed the hypothesis that more intense chemotherapy (i.e. aE and CMF) led to more severe side-effects with worse impact on patient functioning. Patients treated with aE reported more problems in 9 out of 23 QOL scales (including Global Health/QOL reported previously). Fatigue, treatment side effects, physical, role and social functions were all worse at the end of treatment. To our knowledge, for the first time we demonstrated that this impact did not last and was not detectable 12-months after starting chemotherapy. CMF was associated with worse physical side effects than capecitabine and led to deterioration in physical, role and social functioning (10 of 23 QOL scales worse). These differences persisted at 12 and 24-months, contrary to our hypothesis of an expected recovery by 12-months. Responder analysis was implemented to understand if the differences were clinically significant. This showed that in the aE and CMF groups more patients had a clinically meaningful deterioration at the end of treatment compared to E and capecitabine respectively. Psychological distress measured by HADS, was different only in the CMF group where HADS-Depression was worse. This was not related to a change in menopausal status. Mastectomy was associated with higher anxiety and worse emotional function than wide local excision, but no impact on body image or sexual functioning was detected. The emotional impact may be related to the larger tumours at diagnosis, perceived risk and fear of recurrence, but this was not assessed in the trial.

Our findings that dose-dense (accelerated) epirubicin chemotherapy had more significant subjective toxicity and worse impact on patient functioning at the end of treatment are consistent with the QOL results from a tailored dose-dense chemotherapy trial comparing sequential dose-dense epirubicin-cyclophosphamide followed by docetaxel with standard chemotherapy (FEC-docetaxel) [16]. At the end of treatment, 13 of 15 symptoms and functions, measured by EORTC QLQ-C30, were worse in the dose-dense group. There was no long-term follow-up in the trial beyond treatment end. To our knowledge, we report the first long-term data showing that the increased subjective toxicity and functional limitations are temporary with recovery by 12-months.

This data is important to present and future patients and clinicians. The individual patient data meta-analysis (which included TACT2 results) confirmed a clinically significant 14% improvement in population outcomes from accelerated anthracycline therapy in early breast cancer, but there were limited QOL or toxicity data to help patients make an informed choice regarding cost-benefit balance between accelerated and standard chemotherapy [8]. The pivotal randomized trial of dose-dense chemotherapy (Intergroup Trial C9741/Cancer Leukemia Group B Trial 9741) evaluated toxicity in a subset of patients and did not include a QOL study [17]. The trial of FEC-docetaxel tailored dose-dense chemotherapy did not lead to better recurrence-free survival but resulted in increased

haematological toxicity and worse QOL during treatment [16]. Recent trial and accompanying editorial questions the value of anthracyclines as part of adjuvant treatment in HER-2 positive cancers [18]. Our robust QOL data, in almost 1000 patients (including 21% Her-2 positive cancers), provide an evidence-base for informing patients about the type and pattern of this additional toxicity, its impact on functioning and QOL during treatment and reassuringly its resolution after treatment.

Capecitabine is considered by practicing oncologists a well-tolerated chemotherapy with a manageable toxicity profile. Our comparison with CMF confirmed this impression. In a trial of older women (≥65 years), adjuvant chemotherapy with Capecitabine showed less physical symptoms, better functioning and QOL than standard adjuvant chemotherapy (CMF or anthracycline-containing), with the differences resolving by 12-months [19,20]. Our results of CMF vs capecitabine comparison in a younger population are consistent with the above, except the 12-months QOL recovery. The differences with the published data may be related to the younger patient population in our trial. We explored if this may be related to the higher amenorrhea rate in CMF vs capecitabine (75% vs 42%) but the only association was with systemic side-effects scale). One non-inferiority trial comparing classical CMF with another oral fluoropyrimidine (uracil-tegafur) showed similar efficacy but better QOL with oral chemotherapy, a finding consistent with out results[21].

Capecitabine is not currently recommended as a standard adjuvant treatment, but following CREATE-X trial it has become standard of care as adjuvant treatment in triple negative breast cancers with poor prognosis and residual disease, following neo-adjuvant anthracycline and/or taxane-containing chemotherapy [9]. ECOG-ACRIN EA1131 trial supported the use of capecitabine versus platinum in patients with residual triple-negative breast cancer after neoadjuvant chemotherapy [22]. The patient-reported outcomes data in EA1131 suggested worse side-effects with capecitabine than platinum at cycle 3, using a different QOL instrument (Functional Assessment of Cancer Therapy- Breast Cancer Simptom Index) and in a relatively small patient sample (n=331, n=296 completing QOL)[23]. However, the changes in QOL were small and resolved after treatment, similar to TACT2 results. The reassuring QOL results from our trial further support shared decision-making in this group of patients.

A strength of the TACT2 trial and its QOL sub-study is a large geographically wide UK sample. The QOL sub-study participating centres were not pre-selected and all patients from those centres were eligible thus reducing the risk of bias. The QOL subset was similar to the total TACT2 sample in baseline clinical and demographic characteristics. Providing detailed data on QOL impacts of 4 different adjuvant treatments, alongside examination of the clinical significance of the differences via responder analysis, is valuable and informative to both patients and clinicians in supporting shared decision-making.

Limitations to this study should be acknowledged. Patient consent rate (85.6%) and compliance with completion of QOL measures (92% provided at least one questionnaire after randomization) is consistent with other similar trials using postal questionnaires over long time-periods. Overview of 14 clinical trials showed compliance rates per study from

84.7% to 97.2% [24]. The compliance was high during the treatment period; it reduced to about 60% at 12 and 24-months. Exploration of patterns of missing data at 24-months showed younger premenopausal patients were less compliant. Therefore the results at 24-months may not reflect their experiences. A weakness of the QOL sub-study design is the change of the data collection time-points during the study, dictated by pragmatism. The longitudinal modelling explored potential impact of the different scheduling and concluded that the results were not different. Another limitation of the QOL sub-study is the analysis of available data without imputations or accounting for intercurrent events. This choice was made as the number of intercurrent events was low, without differences between the trial arms and unlikely to influence the results.

Currently, there is a range of chemotherapy regimens for adjuvant breast cancer treatment. TACT2 trial showed that if taxanes are not indicated or contraindicated, treatment with epirubicin followed by capecitabine in 3-week cycles is effective and well-tolerated option. This detailed QOL analysis supports the main TACT2 trial conclusion. Whilst the TACT2 trial did not itself find a significant improvement for accelerated chemotherapy, the subsequent meta-analysis, found a reduction in breast cancer recurrences. Two-weekly adjuvant chemotherapy is now offered as standard of care in high-risk early breast cancer, but with few data to inform patients about the extent of associated toxicity and impacts on QOL. Our data rectify that information gap, giving patients and clinicians details on the additional symptom and QOL burden, and importantly confirm that this additional burden resolves within 1-year of starting therapy. The favourable QOL data on capecitabine supports its use as further 'rescue' adjuvant treatment after neo-adjuvant chemotherapy with residual disease in patients with triple-negative cancers.

Contributors

GV, PB-L, HE, AMB, PC, RC, AW, PE, RS ,JMB and DC were involved in the study design. DC oversaw the trial, GV oversaw the QOL sub-study. GV, PB-L, HE, DB, AMB, PC, RC, MV, AW, PE, RS were members of the trial management group. PC and GV did the literature searches. GV, JPM, JSH, CE did the data analysis, and GV, JPM, JSH, CE, DC, JMB interpreted the data. GV and JSH accessed and verified the data. GV, PB-L, HE, AMB, PC, RC, MV, AW, GB recruited patients. AMB and GB were principal investigator recruiter and involved with ongoing management decisions on publication, trial development, and manuscript review. GV, JSH, CE, DC and JMB wrote the paper. PB-L, HE, DB, AMB, PC, RC, MV, AW, GB, PE and RS reviewed the drafts. GV, DC and JMB gave final approval of the paper.

Declarations of interest

GV has received support for the present manuscript from the University of Leeds (payment for time working on manuscript), personal fees from Pfizer, Roche (none related to the manuscript) and was a member of the European Organisation for Research and Treatment of Cancer (EORTC) Board of directors (not related to this manuscript). **RC** has received personal fees from Sanofi, ACE Oncology, Amgen and Beigene, patents, planned, issued or pending with Inbiomotion, personal fee from AstraZeneca and stock options in Inbiomotion (biomarker in development). **MV** has received institutional grants from AstraZeneca, Genomic Health, Novartis, Pfizer, Roche, personal fees from Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Novartis, Pfizer, Roche, Seagen and received personal fees for advisory board work for AstraZeneca, Daiichi-

Sankyo, Exact Sciences, Gilead, Lilly, Merck, Novartis, Pfizer, Roche and Seagen. **AW** has received National Institute for Health Research (NIHR) HTA and NIHR institutional grants. **RS** has received a grant from NIHR (salary support). **JMB** has received support for the present manuscript from Cancer Research UK (research costs to the clinical trials offices), and educational grants funding from Roche, Amgen and Pfizer, institutional grants from AstraZeneca, Merck Sharp & Dohme, Puma Biotechnology, Novartis (previously GSK), Eli Lilly, Janssen-Cilag and Clovis Oncology. **DC** has received personal fees from Aptitude Health, Pfizer, Celldex Therapeutics Inc, Carnall Farrar, Astrazeneca, Celgene Corporation, Eli Lilly, Roche, Novartis, Merck Sharp Dohme, PUMA Biotechnology, F. Hoffmann-La Roche AG, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Therapeutics, Genentech Inc, GSK (Glaxo SmithKline), ICON Clinical Research, Prima BioMED, RTI Health Solutions, Synthon Biopharmaceuticals BV : note name change to Byondis April 2020, Succinct Medical Communications, Seagen, SANOFI, Sapience Therapeutics Ltd, Bexon / Zymeworks Biopharmaceuticals Inc., NexGen, IQVIA: Institutional grants from Cancer Research UK, HTA, Breast International Group (BIG), Breast Cancer Institute, European Cancer Organisation. The other authors (JSS, CE, PBL, HE, GB, PE, DB, AMB, PC) declare no competing interests.

Acknowledgments

We thank the patients, their relatives and treating clinicians, and the hospitals who participated in this study. We wish to acknowledge especially the Cancer Clinical Trials Unit, Scotland, Edinburgh, UK for coordinating the collection of the QOL data. We thank Cancer Research UK for funding the study, Amgen, Pfizer, and Roche, for unrestricted educational grants, and the National Institute for Health Research cancer research networks in England and their equivalent NHS R&D-funded networks in Scotland, Wales, and Northern Ireland for “in-kind” support. We thank the members of the independent data monitoring committee and the Clinical Trials and Statistics Unit at the Institute of Cancer Research overarching trials steering committee, and the two co-sponsoring organisations, The Institute of Cancer Research and NHS Lothian. Roche supplied free capecitabine and Amgen provided subsidised pegfilgrastim for trial use.

References

1. Burstein HJ, Curigliano G, Thurlimann B, et al. Customizing local and systemic therapies for women with early breast cancer: the St. Gallen International Consensus Guidelines for treatment of early breast cancer 2021. *Ann Oncol* 2021; **32**(10): 1216-35.
2. Hall E, Cameron D, Waters R, et al. Comparison of patient reported quality of life and impact of treatment side effects experienced with a taxane-containing regimen and standard anthracycline based chemotherapy for early breast cancer: 6 year results from the UK TACT trial (CRUK/01/001). *Eur J Cancer* 2014; **50**(14): 2375-89.
3. Goodwin PJ, Black JT, Bordeleau LJ, Ganz PA. Health-related quality-of-life measurement in randomized clinical trials in breast cancer--taking stock. *J Natl Cancer Inst* 2003; **95**(4): 263-81.
4. Lemieux J, Goodwin PJ, Bordeleau LJ, Lauzier S, Theberge V. Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001-2009). *J Natl Cancer Inst* 2011; **103**(3): 178-231.
5. Del Mastro L, Costantini M, Morasso G, et al. Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. *Eur J Cancer* 2002; **38**(3): 359-66.
6. Poole CJ, Earl HM, Hiller L, et al. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *N Engl J Med* 2006; **355**(18): 1851-62.
7. Cameron D, Morden JP, Canney P, et al. Accelerated versus standard epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil or capecitabine as adjuvant therapy for breast cancer in the randomised UK TACT2 trial (CRUK/05/19): a multicentre, phase 3, open-label, randomised, controlled trial. *Lancet Oncol* 2017; **18**(7): 929-45.
8. Early Breast Cancer Trialists' Collaborative G. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. *Lancet* 2019; **393**(10179): 1440-52.
9. Masuda N, Lee SJ, Ohtani S, et al. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. *N Engl J Med* 2017; **376**(22): 2147-59.
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; **67**(6): 361-70.
11. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85**(5): 365-76.
12. Sprangers MA, Groenvold M, Arraras JI, et al. The European Organization for Research and Treatment of Cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996; **14**(10): 2756-68.
13. EORTC. EORTC QLQ-C30 Scoring Manual. 2001. https://www.eortc.org/app/uploads/sites/2/2018/02/SCmanual.pdf (accessed 2nd April 2022 2022).
14. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res* 2011; **11**(2): 163-9.
15. Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16**(1): 139-44.

16. Foukakis T, von Minckwitz G, Bengtsson NO, et al. Effect of Tailored Dose-Dense Chemotherapy vs Standard 3-Weekly Adjuvant Chemotherapy on Recurrence-Free Survival Among Women With High-Risk Early Breast Cancer: A Randomized Clinical Trial. *JAMA* 2016; **316**(18): 1888-96.
17. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. *J Clin Oncol* 2003; **21**(8): 1431-9.
18. Hurvitz SA. Anthracycline Use in ERBB2-Positive Breast Cancer: It Is Time to Re-TRAIN. *JAMA Oncol* 2021; **7**(7): 975-7.
19. Kornblith AB, Lan L, Archer L, et al. Quality of life of older patients with early-stage breast cancer receiving adjuvant chemotherapy: a companion study to cancer and leukemia group B 49907. *J Clin Oncol* 2011; **29**(8): 1022-8.
20. Muss HB, Berry DA, Cirrincione CT, et al. Adjuvant chemotherapy in older women with early-stage breast cancer. *N Engl J Med* 2009; **360**(20): 2055-65.
21. Watanabe T, Sano M, Takashima S, et al. Oral uracil and tegafur compared with classic cyclophosphamide, methotrexate, fluorouracil as postoperative chemotherapy in patients with node-negative, high-risk breast cancer: National Surgical Adjuvant Study for Breast Cancer 01 Trial. *J Clin Oncol* 2009; **27**(9): 1368-74.
22. Mayer IA, Zhao F, Arteaga CL, et al. Randomized Phase III Postoperative Trial of Platinum-Based Chemotherapy Versus Capecitabine in Patients With Residual Triple-Negative Breast Cancer Following Neoadjuvant Chemotherapy: ECOG-ACRIN EA1131. *J Clin Oncol* 2021; **39**(23): 2539-51.
23. Smith KLZ, F.; Mayer,I.A.;Tevaarwerk,A.J.; Garcia,S.F.; Arteaga,C.L.; SymmansW.F.; Park,B.H.; Burnette,B.L.;Makower,D.F.;Block,M.;Morley,K.A.;Jani,C.R.; Mescher,C.;Dewani,S.J.;Brown-Glaberman,U.;Flaum,L.E.;Mayer,E.L.;Sikov,W.M.;Rodler,E.T.; DeMichele,A.M.;SparanoJ.A.;Wolff,A.C.;Miller,K.D.;Wagner,L.I. Abstract P4-10-02: Patient-reported outcomes in EA1131: A randomized phase III trial of platinum vs. capecitabine in patients with residual triple-negative breast cancer after neoadjuvant chemotherapy. *Cancer Research* 2022; **82**: P4-10-02.
24. Atherton PJ, Burger KN, Pederson LD, Kaggal S, Sloan JA. Patient-reported outcomes questionnaire compliance in Cancer Cooperative Group Trials (Alliance N0992). *Clin Trials* 2016; **13**(6): 612-20.

TACT2 QOL manuscript Tables

Table 1. Baseline characteristics for participants in QOL sub-study and all TACT2 participants.

	Patients consenting for QoL study		Patients not participating in QoL study	
	N = 1281		N = 3110	
	n	%	n	%
Age (years)				
<40	118	*9.2*	272	*8.7*
40-49	417	*32.6*	1048	*33.7*
50-59	473	*36.9*	1094	*35.2*
60-69	260	*20.3*	655	*21.1*
≥70	13	*1.0*	41	*1.3*
Sex				
Female	1273	*99.4*	3098	*99.6*
Male	8	*0.6*	12	*0.4*
Menopausal status				
Pre-menopausal	482	*37.6*	1178	*37.9*
Post-menopausal	798	*62.3*	1928	*62.0*
Not known	1	*0.1*	4	*0.1*
Nodes involved				
0*	586	*45.7*	1468	*47.2*
1-3	494	*38.6*	1286	*41.4*
4-9	144	*11.2*	274	*8.8*
≥10	57	*4.4*	82	*2.6*
ER/PgR Status				
ER positive/PgR positive	564	*44.0*	1476	*47.5*
ER positive/PgR negative	101	*7.9*	275	*8.8*
ER positive/PgR unknown*	289	*22.6*	459	*14.8*
ER negative/PgR positive	15	*1.2*	34	*1.1*
ER negative/PgR negative	292	*22.8*	807	*25.9*
ER negative/PgR unknown	20	*1.6*	59	*1.9*
HER2 status				
Negative	1003	*78.3*	2532	*81.4*
Positive	265	*20.7*	566	*18.2*
Borderline	4	*0.3*	6	*0.2*
Not known	9	*0.7*	6	*0.2*
Phenotype				
ER positive &/or PgR positive, & HER2 negative (luminal)	782	*61.1*	1884	*60.6*
HER2 positive, ER positive, &/or PgR positive	176	*13.7*	351	*11.3*
HER2 positive, ER negative, & PgR negative	89	*7.0*	215	*6.9*
Triple negative	221	*17.3*	648	*20.8*
Not known	13	*1.0*	12	*0.4*
Histological type				
Infiltrating ductal	1074	*83.8*	2586	*83.2*
Infiltrating lobular	113	*8.8*	287	*9.2*
Mixed ductal/lobular	48	*3.7*	103	*3.3*
Other	46	*3.6*	134	*4.3*
Tumour size (cm)				
≤2	526	*41.1*	1276	*41.0*

	Patients consenting for QoL study		Patients not participating in QoL study	
	N = 1281		N = 3110	
	n	%	n	%
>2 & ≤5	683	*53.3*	1662	*53.4*
>5	71	*5.5*	170	*5.5*
Not known	1	*0.1*	2	*0.1*
Tumour grade				
G1	44	*3.4*	131	*4.2*
G2	498	*38.9*	1193	*38.4*
G3	738	*57.6*	1781	*57.3*
Not known	1	*0.1*	5	*0.2*
Vascular invasion				
Yes	503	*39.3*	1200	*38.6*
No	729	*56.9*	1719	*55.3*
Not known	49	*3.8*	191	*6.1*
Definitive surgery				
Wide local excision	680	*53.1*	1708	*54.9*
Mastectomy**	600	*46.8*	1400	*45.0*
Not known	1	*0.1*	2	*0.1*

* - ER status and nodal involvement not known for one patient, assumed to be have been ER positive and to have had zero nodes involved based on their stratification at randomisation

** - Includes patients who had both a WLE and mastectomy

Table 2. Baseline EORTC QLQ-C30, EORTC QLQ-BR23 and Hospital Anxiety and Depression Scale (HADS) scores, by treatment group.

	E-CMF			aE-CMF			E-X			aE-X		
	n	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
HADS scores*												
Anxiety	273	6.4	4.0	273	6.2	4.5	290	6.2	4.0	286	7.0	4.3
Depression	271	3.3	3.1	273	2.8	3.2	290	3.0	2.9	286	3.1	3.3
Total	271	9.7	6.4	273	9.0	7.0	290	9.2	6.2	285	10.1	6.8
HADS score category*	n	%		n	%		n	%		n	%	
HADS Anxiety category												
No case	169	61.9		179	65.6		181	62.4		165	57.7	
Borderline case	60	22.0		48	17.6		71	24.5		66	23.1	
Case	44	16.1		46	16.8		38	13.1		55	19.2	
Total	273	100.0		273	100.0		290	100.0		286	100.0	
HADS Depression category												
No case	244	90.0		244	89.4		263	90.7		255	89.2	
Borderline case	18	6.6		17	6.2		23	7.9		22	7.7	
Case	9	3.3		12	4.4		4	1.4		9	3.1	
Total	271	100.0		273	100.0		290	100.0		286	100.0	
HADS Total score category												
No case	242	89.3		246	90.1		265	91.4		245	86.0	
Case	29	10.7		27	9.9		25	8.6		40	14.0	
Total	271	100.0		273	100.0		290	100.0		285	100.0	
EORTC QLQ C-30 subscale	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**	**n**	**Mean**	**SD**
Physical functioning**	273	89.1	14.7	274	89.8	16.3	290	90.3	13.4	288	89.8	15.2
Role functioning**	273	72.4	28.7	274	77.7	26.6	289	74.3	27.1	288	74.0	29.9
Emotional functioning**	273	73.6	23.5	273	75.1	21.9	290	74.4	21.0	288	72.6	21.8
Cognitive functioning**	273	84.1	21.8	273	84.4	19.9	290	87.5	17.8	288	84.8	18.9
Social functioning**	271	75.0	26.5	273	80.4	24.7	289	78.4	23.9	288	78.3	23.3
Fatigue***	273	25.1	20.7	273	22.1	20.4	290	24.4	19.3	288	23.7	21.5
Nausea and vomiting***	273	3.1	10.1	274	3.8	11.3	290	3.4	9.1	289	3.6	9.5
Pain***	273	19.9	23.1	274	19.5	22.4	290	20.1	21.4	288	20.9	24.7
Dyspnoea***	273	5.9	15.3	273	5.7	15.5	290	5.3	13.7	289	7.6	16.5
Insomnia***	273	33.3	30.1	273	29.8	28.6	290	29.9	29.0	288	32.5	29.2
Appetite loss***	273	9.9	18.6	273	9.8	19.7	290	9.3	18.4	289	8.3	17.6
Constipation***	273	9.9	21.1	273	8.4	18.9	290	9.7	21.3	289	9.8	19.6
Diarrhoea***	273	6.1	15.2	271	6.4	14.9	290	5.9	14.4	289	5.1	14.3

Financial difficulties***	272	18.8	30.1	273	17.3	28.4	289	17.0	27.9	287	18.6	29.7
EORTC QLQ BR23 subscale												
Body image**	268	78.2	25.0	266	79.5	26.5	279	80.2	24.0	282	77.5	26.2
Sexual functioning**	265	22.3	22.9	262	23.4	25.1	276	25.9	27.4	278	24.7	25.6
Sexual enjoyment**	110	65.8	25.3	118	66.4	26.3	132	66.4	27.5	131	67.9	25.6
Future perspective**	266	52.8	29.2	266	55.6	30.4	281	52.2	28.5	281	48.8	29.9
Systemic side-effects***	271	8.3	10.1	271	8.1	10.4	287	7.9	9.5	286	8.0	10.1
Breast symptoms***	273	23.2	18.3	273	21.9	16.3	287	21.8	18.1	288	21.6	16.8
Arm symptoms***	273	23.0	20.3	273	21.5	20.4	288	21.8	19.0	288	22.4	19.6
Hair loss***	271	0.7	5.7	268	0.4	4.5	285	0.6	4.4	285	1.1	8.6

* HADS Scores range from 0 to 21 on each scale, with higher scores indicating more distress. Scores above 11 suggest probable cases of anxiety or depressive illness, and scores between 8 and 10 indicate borderline cases. A combined score of 19 or above is considered indicative of psychological distress.
EORTC Scores range is 0-100.
** Functional scales- high score=Good function.
*** Symptom scales/items High score= Worse symptoms.

Table 3: Cross-sectional comparisons at the end of each treatment phase. E - aE compared at the end of phase 1 treatment; CMF-X compared at the end of phase 2 treatment (i.e. end of the chemotherapy).

	E			aE			p-value	CMF			X			p-value
	n	Mean	SD	n	Mean	SD	(end of Evs.aE)[$]	n	Mean	SD	n	Mean	SD	(end of CMF vs. X)[$]
HADS scores*														
Anxiety	514	5.6	4.22	485	5.2	4.18	0.19	467	5.2	4.20	492	4.9	3.98	0.40
Depression	513	5.0	3.75	485	5.3	4.12	0.33	467	4.8	3.77	492	4.2	3.66	0.0048
Total	513	10.6	7.25	485	10.6	7.50	0.88	467	10.0	7.24	492	9.1	6.79	0.075
QLQ C-30 and BR23 subscales scores**														
Secondary outcomes														
Physical functioning**	511	80.3	18.43	484	76.8	20.38	0.0065	464	76.5	20.17	493	79.6	19.50	0.0048
Role functioning**	511	65.0	29.22	484	56.6	29.74	<0.0001	464	60.2	29.66	493	64.5	29.82	0.013
Fatigue***	512	44.0	25.56	484	50.1	26.30	0.00018	464	48.7	26.56	493	40.8	26.63	<0.0001
Systemic side-effects***	515	39.1	19.65	487	43.8	19.78	0.00012	468	35.2	18.72	494	29.0	18.10	<0.0001
Sexual functioning**	484	16.9	20.82	466	16.6	22.33	0.36	441	15.5	20.64	463	19.6	23.20	0.0053
Exploratory analysis														
Emotional functioning**	512	76.0	22.73	484	74.3	23.22	0.19	465	78.2	23.24	493	79.7	21.12	0.500
Cognitive functioning**	512	75.0	23.03	484	75.2	22.79	0.94	465	69.6	24.93	493	76.1	23.15	<0.0001
Social functioning**	512	67.3	26.54	484	61.8	29.35	0.0053	465	65.3	29.13	493	70.6	27.25	0.0043
Nausea and vomiting***	512	14.6	19.09	484	20.5	20.42	<0.0001	464	15.3	21.42	493	12.2	18.24	0.027
Pain***	512	17.0	23.36	484	20.8	25.39	0.01	465	16.8	24.73	493	18.5	23.94	0.074
Dyspnoea***	511	20.0	25.25	484	22.5	26.72	0.16	463	27.7	28.04	490	18.3	26.60	<0.0001
Insomnia***	510	33.1	31.20	484	36.4	30.37	0.042	464	41.0	30.68	491	32.3	30.59	<0.0001
Appetite loss***	511	22.2	27.51	483	30.4	30.76	<0.0001	463	22.3	28.19	493	19.9	27.24	0.16
Constipation***	512	23.3	30.06	484	31.1	31.52	<0.0001	464	22.9	28.80	491	11.7	21.62	<0.0001
Diarrhoea***	512	11.7	20.79	483	13.8	23.77	0.308	464	19.3	28.10	493	20.4	28.72	0.58
Financial difficulties***	510	24.8	31.60	483	22.0	32.29	0.046	464	28.0	33.81	492	24.9	32.50	0.15

Body image**	513	61.9	29.66	486	62.6	29.76	0.63	461	64.4	30.69	490	68.9	29.03	0.027
Sexual enjoyment**	174	52.5	26.88	157	54.8	27.99	0.39	154	54.1	29.29	183	55.4	28.49	0.64
Future perspective**	513	54.1	31.20	484	56.1	30.73	0.32	463	53.0	31.48	489	54.7	31.31	0.39
Breast symptoms***	515	13.2	13.90	487	12.3	13.80	0.27	468	11.9	13.94	492	12.4	14.40	0.55
Arm symptoms***	514	18.3	19.65	486	18.5	21.88	0.41	468	13.8	17.39	494	14.2	17.81	0.91
Hair loss***	495	38.9	39.14	472	43.0	39.50	0.099	459	16.8	32.62	486	14.3	30.84	0.15

* HADS Scores range from 0 to 21 on each scale, with higher scores indicating more distress. Scores above 11 suggest probable cases of anxiety or depressive illness, and scores between 8 and 10 indicate borderline cases. A combined score of 19 or above is considered indicative of psychological distress.

** Functional scales- high score=Good function. Scores range is 0-100.

*** Symptom scales/items High score= Worse symptoms. Scores range is 0-100.

$ - p-values from Mann-Whitney non-parametric test

Reporting checklist for randomised trial.

Based on the CONSORT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the CONSORTreporting guidelines, and cite them as:

Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

		Reporting Item	Page Number
Title and Abstract			
Title	#1a	Identification as a randomized trial in the title.	1
Abstract	#1b	Structured summary of trial design, methods, results, and conclusions	2
Introduction			
Background and objectives	#2a	Scientific background and explanation of rationale	5
Background and objectives	#2b	Specific objectives or hypothesis	5
Methods			
Trial design	#3a	Description of trial design (such as parallel, factorial) including allocation ratio.	6
Trial design	#3b	Important changes to methods after trial	6,7 QOL data

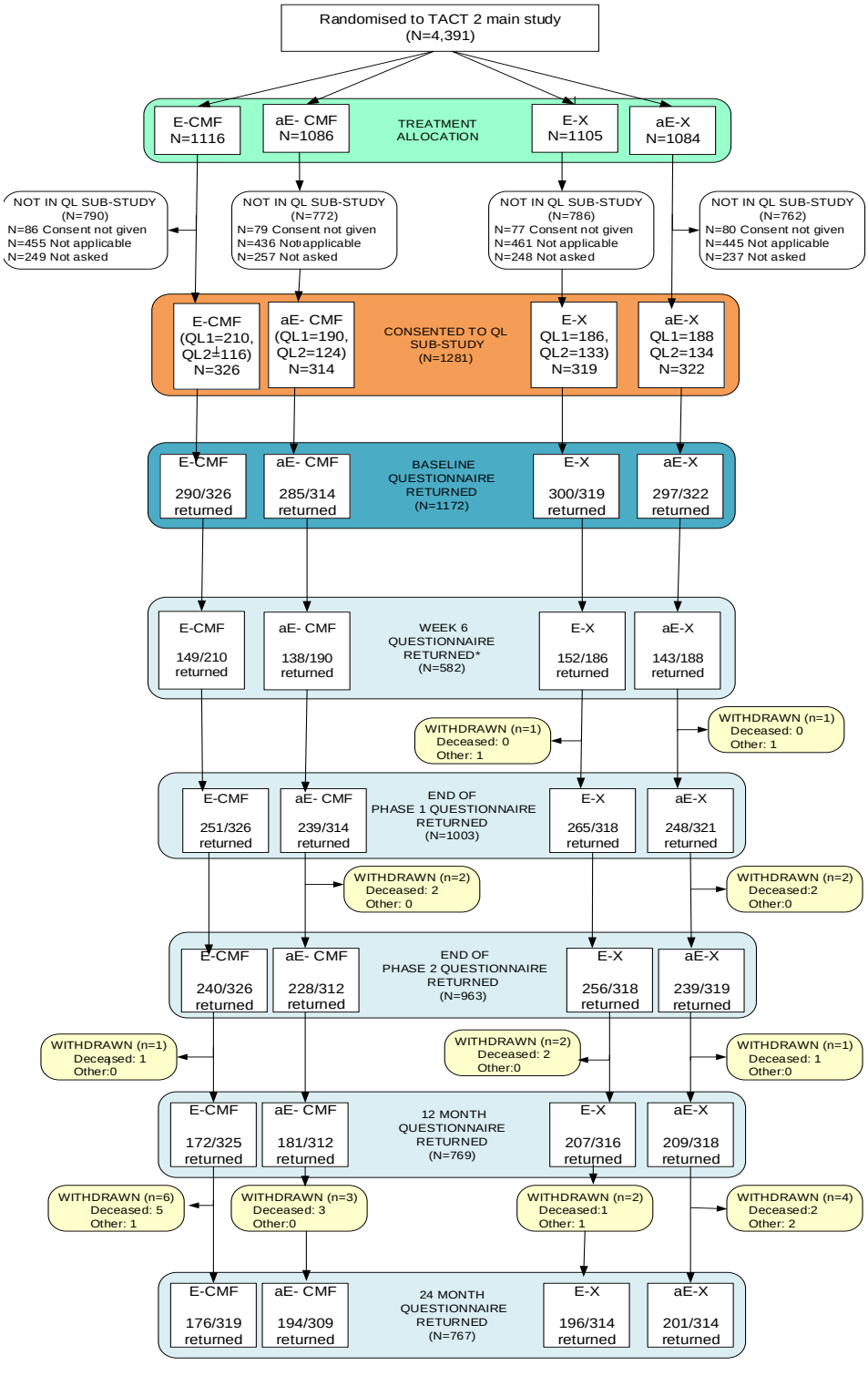
		commencement (such as eligibility criteria), with reasons	collection
Participants	#4a	Eligibility criteria for participants	6
Participants	#4b	Settings and locations where the data were collected	6,7
Interventions	#5	The experimental and control interventions for each group with sufficient details to allow replication, including how and when they were actually administered	6
Outcomes	#6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	6,7
Outcomes	#6b	Any changes to trial outcomes after the trial commenced, with reasons	n/a
Sample size	#7a	How sample size was determined.	7
Sample size	#7b	When applicable, explanation of any interim analyses and stopping guidelines	n/a
Randomization – Sequence generation	#8a	Method used to generate the random allocation sequence. Page **6**	
Randomization - Sequence generation	#8b	Type of randomization; details of any restriction (such as blocking and block size) page **6**	
Randomization - Allocation concealment mechanism	#9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	6
Randomization - Implementation	#10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to interventions	6
Blinding	#11a	If done, who was blinded after assignment to interventions (for example, participants, care	n/a

		providers, those assessing outcomes) and how.	
Blinding	#11b	If relevant, description of the similarity of interventions	n/a
Statistical methods	#12a	Statistical methods used to compare groups for primary and secondary outcomes	7,8
Statistical methods	#12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8, 9
Results			
Participant flow diagram (strongly recommended)	#13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1 CONSORT
Participant flow	#13b	For each group, losses and exclusions after randomization, together with reason	9, appendix
Recruitment	#14a	Dates defining the periods of recruitment and follow-up	9
Recruitment	#14b	Why the trial ended or was stopped	n/a
Baseline data	#15	A table showing baseline demographic and clinical characteristics for each group	Table 1 p1
Numbers analysed	#16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Tables 2,3
Outcomes and estimation	#17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 3
Outcomes and estimation	#17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	n/a
Ancillary analyses	#18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	10-12
Harms	#19	All important harms or unintended effects in each	n/a

		group (For specific guidance see CONSORT for harms)	
Discussion			
Limitations	#20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	14
Generalisability	#21	Generalisability (external validity, applicability) of the trial findings	12-13
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	12-14
Registration	#23	Registration number and name of trial registry	3,10
Other information			
Interpretation	#22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	13-15
Registration	#23	Registration number and name of trial registry	2
Protocol	#24	Where the full trial protocol can be accessed, if available	
Funding	#25	Sources of funding and other support (such as supply of drugs), role of funders	2, 9

TACT2 QOL manuscript Figures

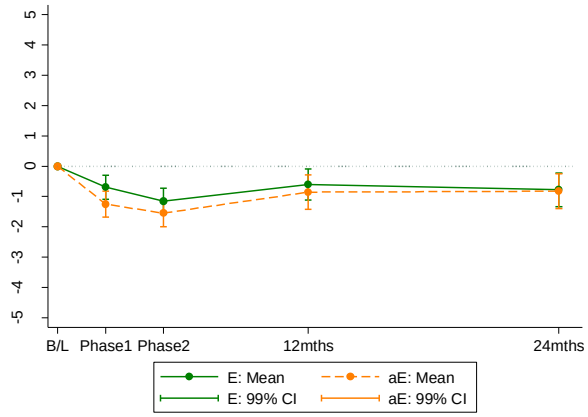
Figure 1. CONSORT Trial profile



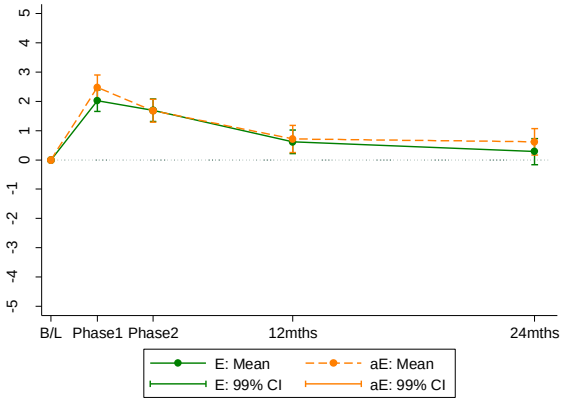
*Consent not given- patients approached for QOL sub-study but declined participation; Not applicable – patients from non-QOL centres; Not asked – patients in QOL centre but recruited during the pause between Stage QL1 and Stage QL2 in QOL sub-study
Withdrawn Other: All due to patient request, except one – moved abroad.

Figure 2. QOL scores mean change and 99%CI from baseline by E/aE. *For HADS scales and EORTC Symptom scales "change>0" means worse scores overtime; For EORTC functional scales "change <0" means worse scores overtime

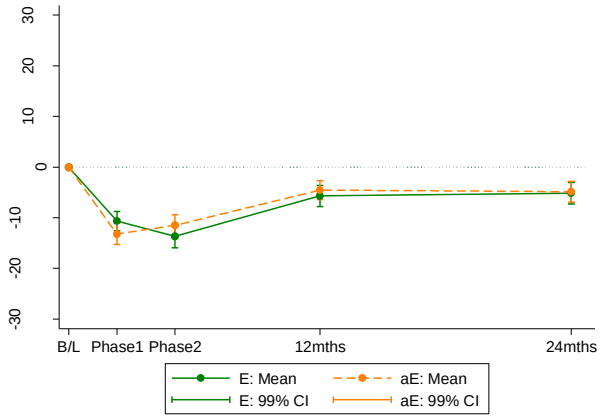
2a. HADS Anxiety*



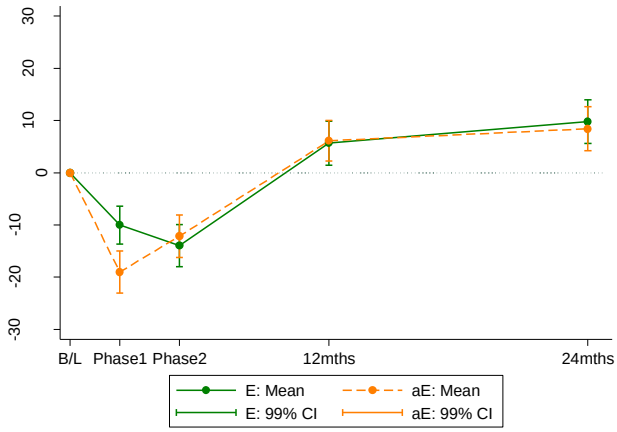
2b. HADS Depression*



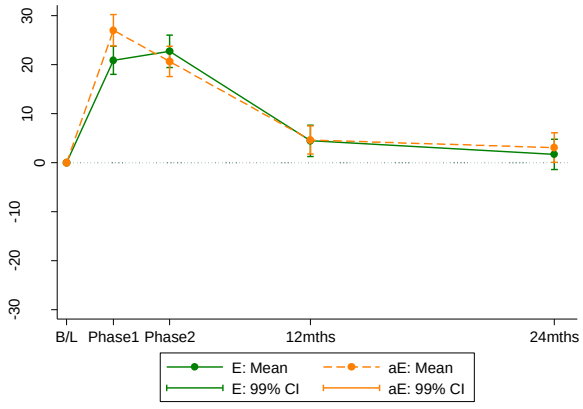
2c. Physical Function**



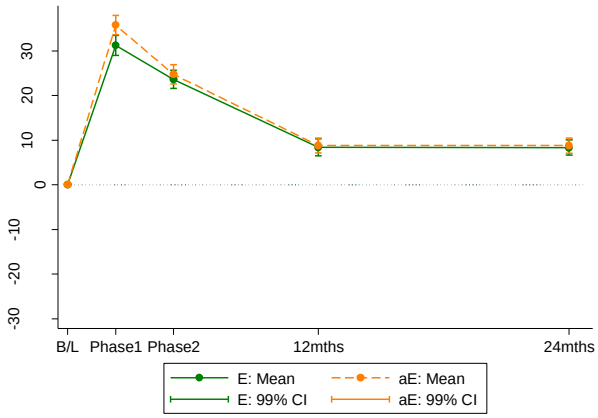
2d. Role Function**



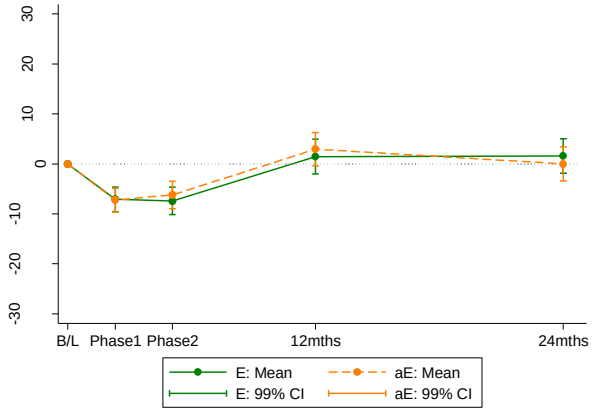
2e. Fatigue*



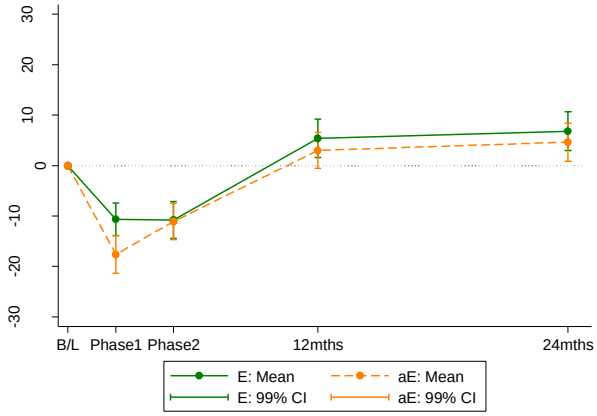
2f. Systemic side-effects scale*



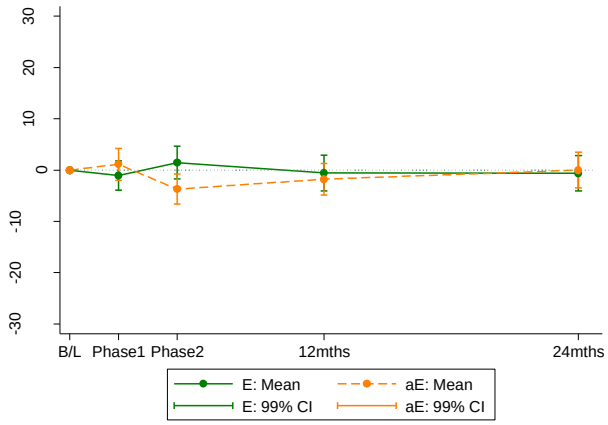
2g. Sexual function**



2h. Social Function**



2i. Pain*



2j. Constipation*

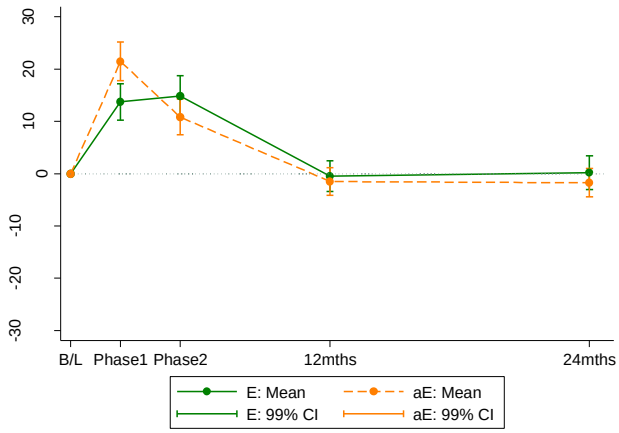
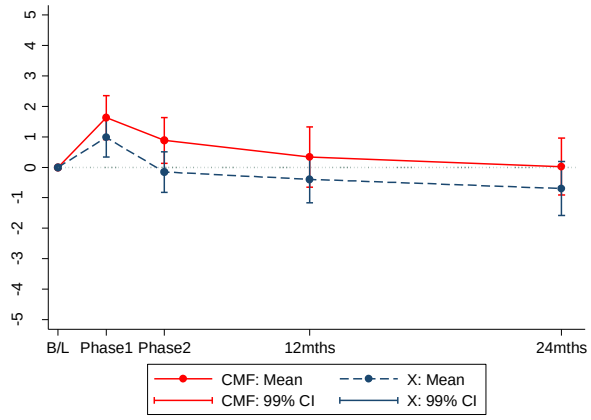
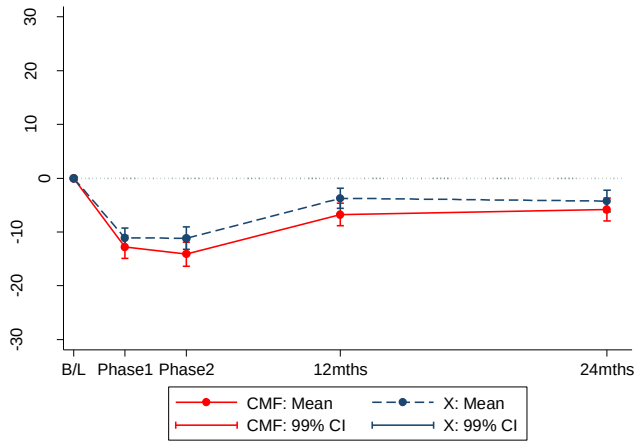


Figure 3. QOL scores mean change and 99%CI from baseline by CMF/X. *For HADS scales and EORTC Symptom scales "change>0" means worse scores overtime; **For EORTC functional scales "change <0" means worse scores overtime

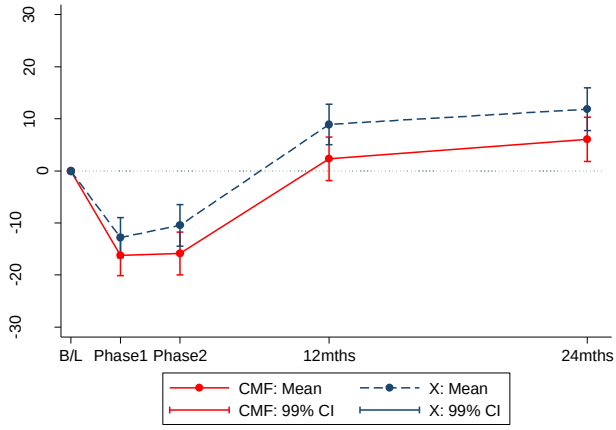
3a. HADS Total score*



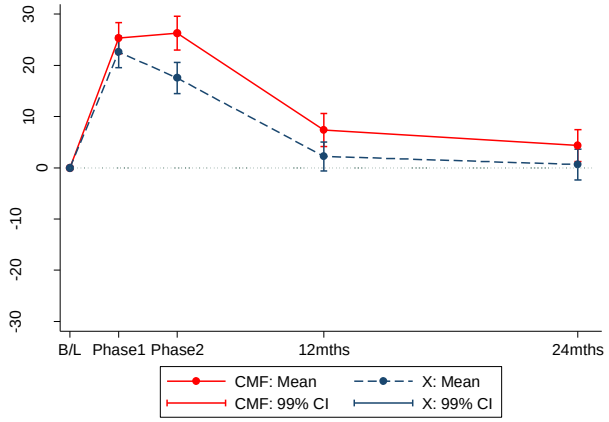
3b.Physical Function**



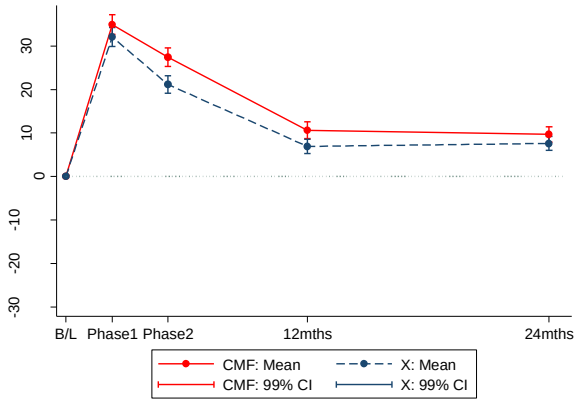
3c. Role function**



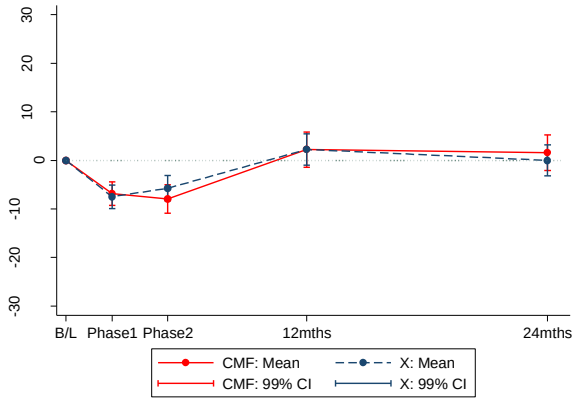
3d. Fatigue*



3e. Systemic side-effects scale*

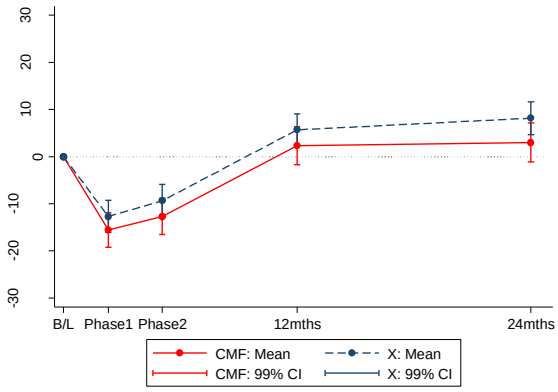


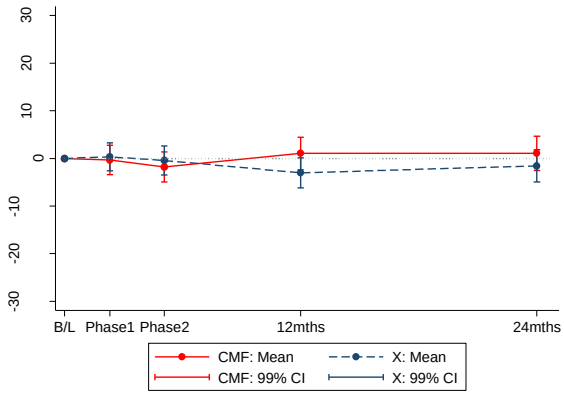
3f. Sexual Function**



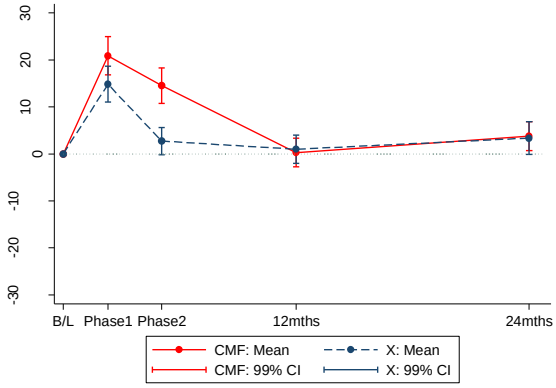
3h. Pain*

3g. Social function**





3i. Constipation*



3j. Dyspnoea* (exploratory analysis)

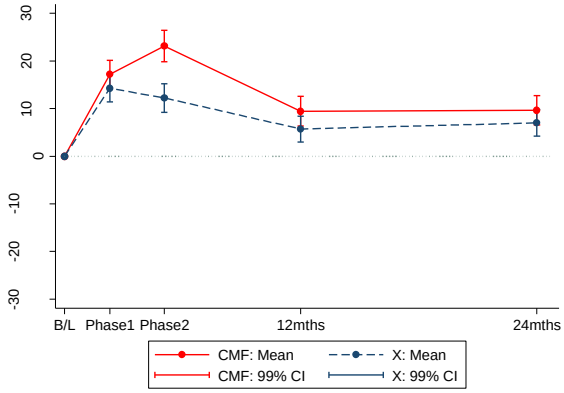
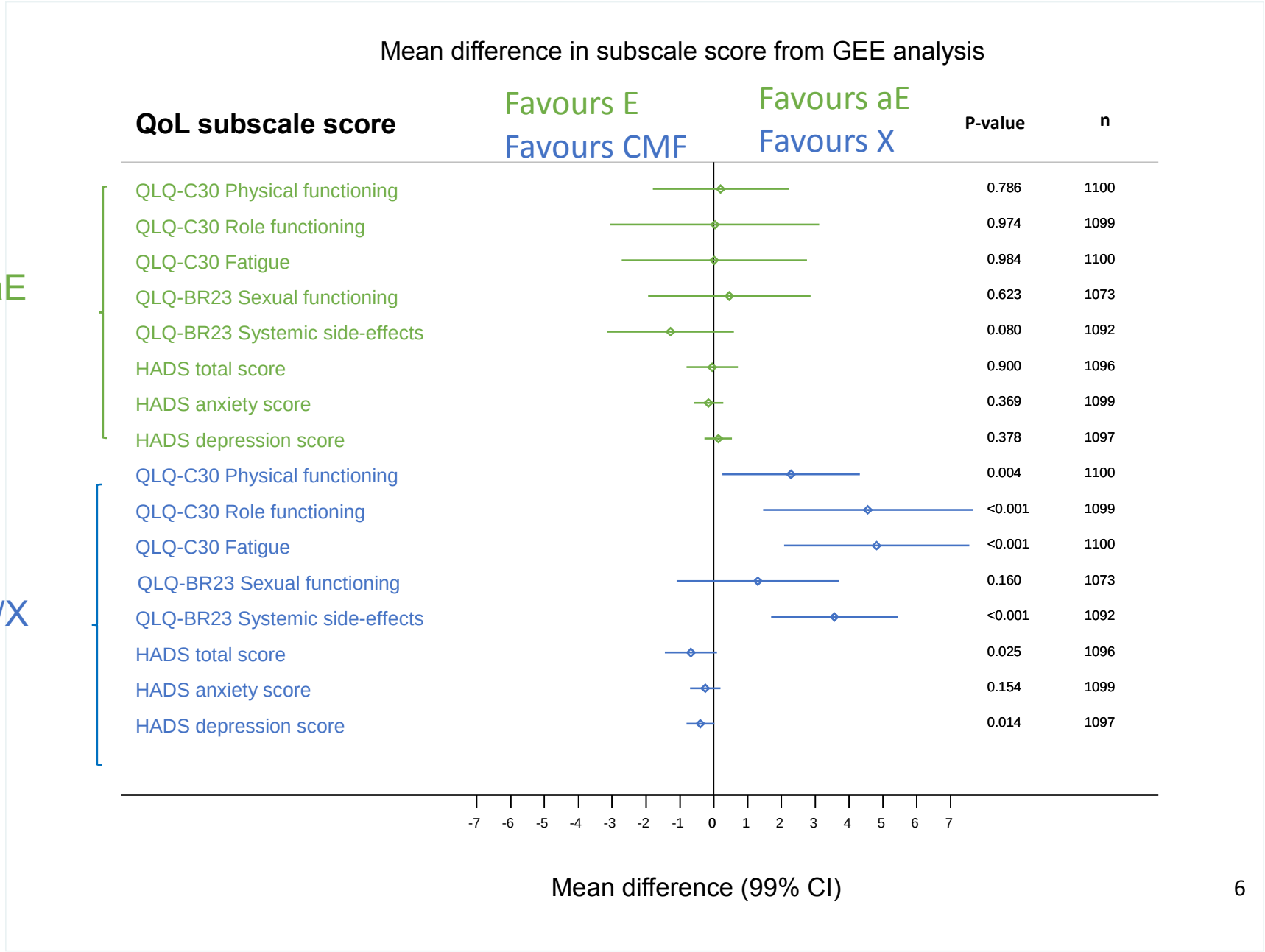


Figure 4. Forest plots of mean difference (99%CI) in subscale score from GEE analysis



Trial of Accelerated Adjuvant ChemoTherapy with Capecitabine in Early Breast Cancer (TACT2)

This trial is part of the NCRN portfolio, endorsed by CTAAC and co-sponsored by Lothian Health Board and The Institute of Cancer Research

Protocol Version: 6, 29th April 2015
MREC ref: 04/MRE00/88
CTA number: 17844/0204/001-0031
EudraCT number: 2004-000066-13
ISRCTN68068041

ADMINISTRATION

This protocol is a controlled document and should not be copied, distributed or reproduced without the written permission of the ICR-CTSU.

Chief Investigator:
David Cameron
Edinburgh Cancer Research Centre
Tel: 0131 777 3512
Fax:0131 777 3520
Email: D.cameron@ed.ac.uk

Clinical co-ordinators:
Peter Canney
Retired
Email: pg.canney@me.com
Peter Barrett-Lee
Velindre NHS Trust, Whitchurch
Cardiff CF14 2TL
Tel.: 029 2031 6914 Fax: 029 2031 6267
Email: Peter.Barrett-Lee@velindre-tr.wales.nhs.uk

The ICR-Clinical Trials & Statistics Unit (an NCRI cancer clinical trials unit) has overall responsibility for the conduct of the trial.

Statistician: Judith Bliss
Email: Judith.Bliss@icr.ac.uk
Trial Management: Jane Banerji
Email:Jane.banerji@icr.ac.uk

ICR-CTSU, Section of Clinical Trials
Institute of Cancer Research,
Cotswold Road, Sutton,
Surrey SM2 5NG
Tel: 020 8722 4349 Fax: 020 8722 4368

The trial is also managed on a day to day basis by the following trials offices on behalf of their regional research groups:

Cancer Clinical Trials Unit Scotland (CaCTUS) *(also running the Quality of Life Study)*
Gyle Square, 1 South Gyle Crescent, Edinburgh EH12 9EB
Tel: 0131 275 7061

Northern & Yorkshire Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, LS2 9JT
Tel: 0113 343 8088

CR-UK Clinical Trials Unit, Institute for Cancer Studies, Vincent Drive, Edgbaston, Birmingham, B15 2TT
Tel: 0121 414 3057/4371

Quality of Life Study Coordinator: Galina Velikova (Leeds)
Quality of Life Study (Protocol Design) : Penny Hopwood (Manchester)
Biological studies: John Bartlett (Toronto, Canada and Edinburgh)
Health Economics Study Coordinator: David Bloomfield (Brighton)

Protocol Working Group: John Bartlett (Edinburgh), David Bloomfield (Brighton), Murray Brunt (Stoke), Robert Coleman (Sheffield), Helena Earl (Cambridge), Paul Ellis (London), Steve Johnston (London), Robert Leonard (Swansea), Chris Poole (Birmingham), Anne Robinson (Southend), Ian Smith (London), Robert Stein (London), Chris Twelves (Bradford), Mark Verrill (Newcastle), Andrew Wardley (Manchester)

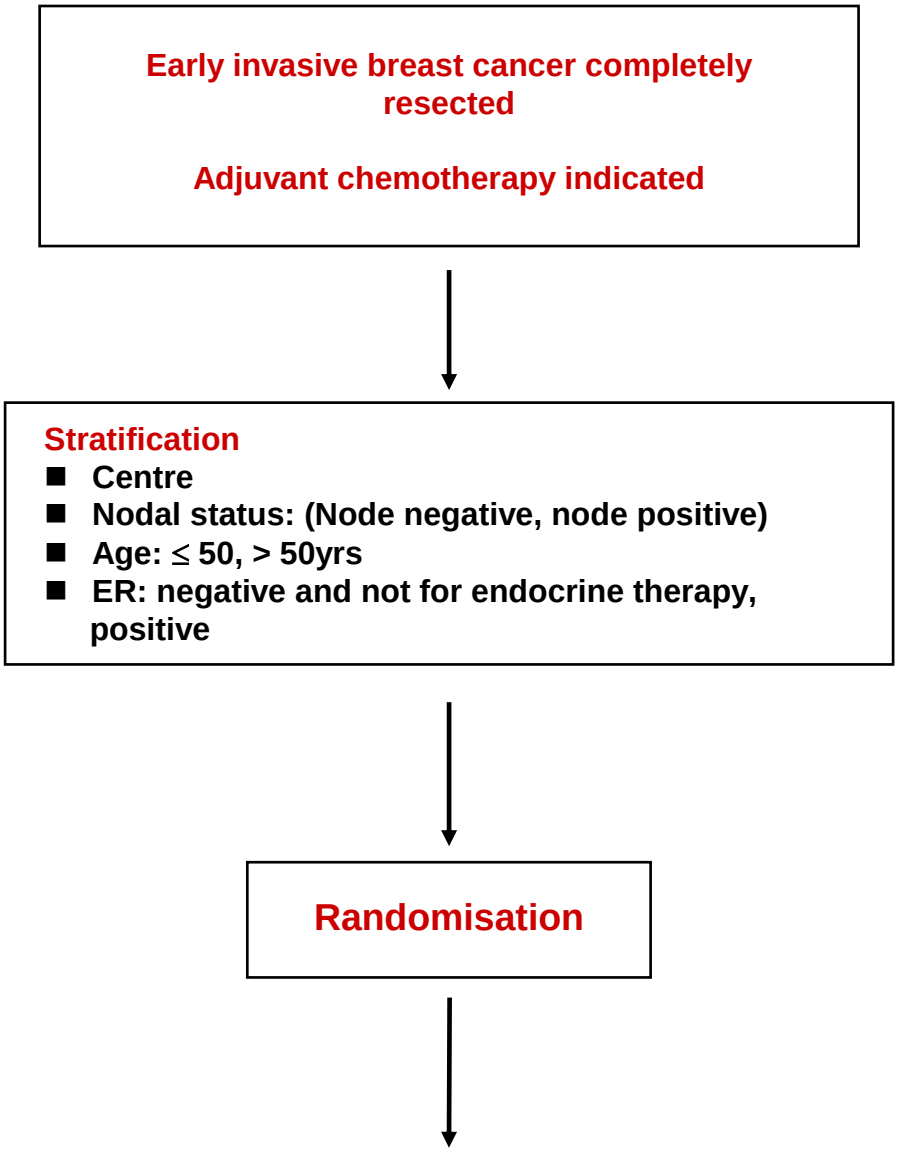
TACT2 protocol version 6 approved by:

Signed…… date …29th April 2015

This clinical trial protocol is intended to provide guidance and information only for the conduct of the TACT2 Trial in participating centres. It is not for use as a guide for the management of other patients outside of the trial. Protocol amendments will be circulated to participating centres as they occur.

Contents **Page**

TRIAL SCHEMA



① 4 cycles of epirubicin every 3 weeks followed by 4 cycles of Classical/Bonadonna CMF	② 4 cycles of epirubicin every 2 weeks with pegylated GCSF support followed by 4 cycles of Classical/Bonadonna CMF
③ 4 cycles of epirubicin every 3 weeks followed by 4 cycles of oral capecitabine	④ 4 cycles of epirubicin every 2 weeks with pegylated GCSF support followed by 4 cycles of oral capecitabine

INTRODUCTION

Breast cancer is the most common malignancy to afflict women in the Western World. There are over 41,000 new cases each year in the UK alone, with an annual mortality of approximately 13,000 [1]. One woman in nine is affected at some time in her life. Whilst the age incidence curve for breast cancer is similar to most other solid tumours, it remains the major killer of women in childbearing years. Besides the morbidity and mortality caused to the woman herself, breast cancer also has profound psychological and economic consequences for the family. More effective treatments are urgently required. Our knowledge of the natural history of this disease suggests that any significant improvement in outcome will depend upon the development of more effective adjuvant therapy for women presenting with early stage disease [2]. This may present a major challenge to NHS resources [3-5], and behoves more precise identification of individual risk as well as elucidation of those factors predicative of treatment benefit.

BACKGROUND & RATIONALE

ADJUVANT THERAPY FOR EARLY STAGE BREAST CANCER

Although early stage breast cancer is by definition grossly limited to the breast and ipsilateral axillary nodes and amenable to surgical resection, occult local and systemic micrometastatic deposits may later develop into a clinically detectable recurrence, and eventually prove fatal. Twenty-year follow-up studies of women presenting with early stage breast cancer in the UK and North America in the 1940's established the limitations of purely loco regional treatment in modifying the natural history of early stage disease [6,7]. Together with preclinical work, which defined susceptibility of micrometastases to chemotherapy [8], these studies provided the justification for the clinical development of systemic adjuvant chemotherapy in the 1970's [9].

Thirty years on, there is now an incontrovertible body of evidence to demonstrate the success of this endeavour. In an overview of 56 trials of prolonged polychemotherapy versus no chemotherapy involving 28,000 women, the Early Breast Cancer Clinical Trialists' Collaborative Group analyses have confirmed that adjuvant chemotherapy reduces the annual odds of recurrence by 23.4% (SE 1.9), and the odds of death by 15% [10]. This reduction in recurrence emerges chiefly during the first 5 years of follow-up, whereas the survival advantage grows throughout the first 10 years. Subgroup analyses of these data have provided further information about relative benefit from treatment, by axillary lymph node involvement, age, menopausal status, oestrogen receptor (ER) status.

The 1998 Oxford Overview sub-group analyses

Nodal Status

The proportional reduction in risk of recurrence afforded by chemotherapy is similar for women with node-negative and node-positive disease. The 10-year survival of those with node-negative disease is increased from 71% to 78% (an absolute benefit of 7%); the 10-year survival of those with node-positive disease increases from 42% to 53% (an absolute benefit of 11%).

Age

In women aged 50-69 years, the proportional reduction in mortality is smaller than that observed in younger women, 10-year survival of node-negative women increasing from 67% to 69% with polychemotherapy and for node positive disease, the 10-year survival increases from 46% to 49%.

Tumour ER status

Amongst women aged under 50, the overview shows substantially reduced risk of recurrence with combination chemotherapy, both for those with ER-poor disease (40% [SD 7]) and those with ER-positive tumours (33% [SD 8]). These figures were not significantly different from one another. By contrast, among women aged 50-69, the proportional reduction in recurrence appeared to be nearly twice as large in women with ER-poor disease (30% [SD 5]) as in those with ER-positive disease (18% [SD 4]), and the difference between these effects was conventionally significant (heterogeneity between proportional reductions $\chi 21=4{\cdot}5$; $2p=0{\cdot}03$).

The effects of polychemotherapy on recurrence also appeared to be somewhat smaller for women with ER-positive disease when the two age groups were combined (heterogeneity, stratified for age, $\chi 21=4{\cdot}9$; $2p=0{\cdot}03$). However, in both age ranges, the reduction in recurrence among women with ER-positive disease was highly significant (both $2p<0{\cdot}00001$), indicating that in neither age range can such hormone-receptor measurements discriminate a group of women who would fail to benefit from treatment.

Treatment comparisons: anthracyclines

The EBCTCG identified 11 randomised trials, involving a total of nearly 7000 patients, which compare anthracycline-containing regimens, such as FAC or FEC, versus CMF alone. Taken together, the addition of anthracyclines yielded a further 12% (SD 4) proportional reduction ($2p=0{\cdot}006$) in the odds of recurrence, with no significant heterogeneity between the effects seen in the different trials. There was also a marginally significant 11% (SD 5) proportional reduction in mortality with the anthracycline-containing regimens ($2p=0{\cdot}02$) at 5 years.

MORE RECENT ADJUVANT STUDIES

Three more recent randomised trials have been reported none of which were available for incorporation in the 1998 Oxford Overview.

The first of these studies (CAN-NCIC-MA-5) randomised 716 pre-and peri-menopausal women lymph node positive tumours to either six cycles of FEC-120 (epirubicin 60mg/m^2, d 1 and 8; oral cyclophosphamide 75 mg/m^2 /d, d 1-14; 5-fluorouracil 500 mg/m^2 i.v. d1 and 8; q 28 days) or classical CMF [11]. The median age of the study population was 45 years. Approximately 60% of patients had 1 - 3 involved nodes, and approximately 40% had $\geq$ 4 nodes involved with tumour. Patients in the epirubicin-treated group had a significantly increased 5-year relapse-free survival rate (62% versus 53%) and an increased 5-year overall survival (77% versus 70%) compared with those treated with classical CMF.

A second study (FRE-GFEA-05) compared a higher dose epirubicin-containing regimen (FEC-100; epirubicin 100 mg/m^2 i.v., cyclophosphamide 500 mg/m^2 i.v., 5-Fluorouracil 500 i.v. mg/m^2, q 21 d) with a lower dose epirubicin-containing regimen (FEC-50; epirubicin 50 mg/m^2 i.v.; cyclophosphamide 500 mg/m^2 i.v.; 5-Fluorouracil 500 i.v. mg/m^2; q 21 d) in 565 pre- and postmenopausal women with either ≥4 nodes involved, or 1 to 3 node-positive if tumours were ER-negative/PgR-negative, with a histological grade of 2 or 3 [12]. The median age was 51 years and approximately half of the patients were postmenopausal. Patients treated with the higher-dose epirubicin regimen had a significantly greater 5-year relapse-free survival rate (65% versus 52%, log-rank p=0.007) and 5-year overall survival (76% versus 65%, log-rank p=0.007) than patients given the lower-dose epirubicin regimen. The overall reduction in risk of relapse was 32%. The relative reduction in the risk of death was 31% [12].

Although neither trial was powered for subset analyses, improvements in RFS and OS were observed both in patients with 1-3 nodes positive and in those with ≥ 4 nodes involved when comparing the FEC-120 or FEC-100 groups with their respective controls. Furthermore, in the dose intensity study, similar improvements in RFS and OS were observed in both pre- and postmenopausal women treated with FEC-100 compared with FEC-50.

The third is the largest ever adjuvant anthracycline study, the prospectively planned meta-analysis of the two UK NEAT trials, which compared the sequential epirubicin-CMF (E-CMF) regimens with CMF. Both these trials show a statistically significant benefit for E-CMF over CMF, and have a combined HR of 0.7 (0.58 – 0.85 95% c.i.) for disease-free survival and 0.64 (0.51 – 0.81 95% c.i.) for overall survival (ASCO 2003 abstract 13).

As a result of these data from the NEAT trials, many UK breast oncologists feel that the sequential E-CMF regimen should be the standard anthracycline regimen, against which alternatives should be compared. It is clear however that there remains significant toxicity associated with the CMF part, with for example, all treatment related deaths in the NEAT studies occurring during administration with CMF [13].

ACCELERATED CHEMOTHERAPY

After the failure of pure dose escalation to improve upon the efficacy of adjuvant chemotherapy, attention has switched to increased frequency of administration, or so called dose dense chemotherapy. The limiting toxicity is usually myelosuppression, but this can be circumvented by the use of Granulocyte Colony Stimulating Factors (GCSF). This approach has proved effective in both small cell lung cancer and lymphoma, but until recently there were no substantive data in breast cancer [14,15,16]. This has changed with the preliminary reports of the CALGB9741 trial, which has shown an improvement in disease-free survival if AC followed by paclitaxel is given at a 2-weekly rather than the conventional 3-weekly interval with GCSF support [17]. The data published in 2003 were based on a pre-planned 3-yearly analysis rather than a pre-defined number of events, and as such there have been insufficient events to detect the difference originally hypothecated. However, coupled with the reported benefits seen in small cell lung cancer and lymphoma, these data suggest further testing is needed. It should also be noted, that in keeping with the studies in small

cell lung cancer and lymphoma, accelerated therapy appears to be associated with less neutropenia than 3-weekly therapy. This was confirmed in an Italian randomised trial of 1214 women presented at the 2003 San Antonio Breast Cancer Symposium, in which there were NO cases of febrile neutropenia in the women randomised to two-weekly FE60C supported by GCSF (Venturini et al SABCS 2003 abstract 12). This same study reported a survival advantage for this approach in women under the age of 50.

The availability of pegylated GCSF has the potential to further reduce the incidence of febrile neutropenia, as it has been recently reported that as compared to conventional daily GCSF (the preparation used in the above studies of accelerated chemotherapy), it may reduce the incidence of neutropenic sepsis by up to 35%.

CAPECITABINE (XELODA®)

This oral 5-FU prodrug has recently gained UK licence and NICE approval for use in advanced breast cancer. No major phase III studies comparing it to other established regimens have been conducted, but the data that are available report little difference between the response rate to this drug and either i.v. CMF or i.v. paclitaxel [18,19]. Similarly there are few robust reports on its tolerability, but it has rapidly become one of the standard regimens to be used in advanced disease after failure of anthracyclines and taxanes.

Of greater interest is the biology of this agent. The final step in its conversion to the active moiety, 5-FU, requires the enzyme thymidine phosphorylase. This is often preferentially expressed in tumours, increasing the potential therapeutic index. A number of anti-cancer therapies appear to up regulate this agent, and recent data suggest that epirubicin is one such cytotoxic agent [20].

It is therefore an attractive drug to use: it requires no intravenous administration, rarely causes neutropenia or other toxicities requiring hospital admission. Given after epirubicin there is the potential added advantage that any remaining micro-metastatic disease is “primed” for increased sensitivity to this agent.

MALE BREAST CANCER

This study will be the first study of adjuvant chemotherapy of which we are aware for which male patients are eligible. Breast cancer is much rarer in men, occurring with about 0.5 – 1% of the frequency of women. However the available literature suggests that matched stage for stage their outcome is similar, and they are managed in much the same manner. There are recent UK studies that have permitted male patients including the currently recruiting “Will Weekly Win” taxol trial, and therefore TACT2 represents a unique opportunity to generate some data from a randomised trial in this hitherto poorly studied subgroup of breast cancer patients.

TRIAL DESIGN

A randomised, phase III clinical trial with a 2 x 2 factorial design addressing two hypotheses:
(1) that accelerating epirubicin will improve the efficacy of the sequential schedules (based originally on the NEAT epirubicin/CMF schedule).

(2) that the substitution of CMF by capecitabine will not be detrimental to patient outcome but will offer advantages in Quality of Life and/or toxicity.

PRIMARY ENDPOINT:

- Time to Recurrence

SECONDARY ENDPOINTS:

- Overall survival (OS)
- Distant disease-free survival (DDFS)
- Disease Free Survival as defined by the STEEP criteria (21)
- Tolerability (including Serious adverse events (SAE)), dose-intensity and toxicity
- Detailed Toxicity and Quality of Life in the subset of patients studied

For the survival-based endpoints (DFS, OS, DDFS) the nominal time-point of interest will be 5 years after randomisation.

TRIAL PROCEDURES

STAGING INVESTIGATIONS

Required staging investigations will be minimal and in keeping with standard UK practice in breast cancer management. All patients should have a FBC, biochemical screen, to include liver function tests, creatinine and serum calcium. A CXR is required for all patients with 4 or more positive axillary nodes, and recommended (but not mandated) for all other patients. Further staging investigations will be performed if considered to be clinically indicated, and an isotope bone scan and/or liver ultrasound are expected to be performed routinely in higher risk patients (such as those with >3-node positive), those with suspicious symptoms and/or abnormal biochemistry.

ELIGIBILITY

INCLUSION CRITERIA

- Histological diagnosis of invasive breast carcinoma
- Completely resected disease with negative surgical margins (apart from deep margin if full thickness resection or involved radial margins following wide local excision if further surgery to the breast is planned on completion of chemotherapy).
- Early stage disease (T0-3 N0-2 M0) without clinical suspicion/evidence of distant metastases on routine staging
- Definite indication for adjuvant chemotherapy
- ECOG status 0 or 1
- Aged over 18 years (no upper age limit)
- Fit to receive any of the trial chemotherapy regimens, with adequate bone marrow, hepatic, and renal function i.e.
    - Hb > 9g/dL; WBC > 3 $\times$ 10^9/L; platelets > 100 x 10^9/L
    - Bilirubin within normal range (unless known Gilbert's disease)
    - AST/ALT ≤ 1.5 x Upper limit of normal (ULN)

    - Albumen within normal range
    - Creatinine ≤ 1.5 x ULN and calculated creatinine clearance using Cockroft-Gault formula > 50 ml/min
    - No active, uncontrolled infection
- Signed TACT2 trial consent form
- Randomisation within 8 weeks of surgery, but ideally within 1 month
- No previous chemotherapy, hormonal therapy or radiotherapy for the treatment of pre-invasive or invasive cancer except:
    - Previous radiotherapy for basal cell carcinoma
    - Previous pre-operative endocrine therapy provided that there was no evidence of progression during this therapy, that it was for less than 6 weeks in duration, and was stopped at least one month prior to trial entry
- No previous malignancy except in the case of DCIS, or basal cell carcinoma or cervical carcinoma in situ, or where the patient has been disease-free for 10 years, and where treatment consisted solely of resection
- Non-pregnant and non-lactating, with no intention of pregnancy during chemotherapy, and prepared to adopt adequate contraceptive measures if pre-menopausal and sexually active
- No concomitant medical, psychiatric or geographic problems that might prevent completion of treatment or follow-up

EXCLUSION CRITERIA

- Only cytological proof of malignancy
- No evidence of invasive breast cancer
- Previous invasive breast cancer or bilateral breast cancer (DCIS or LCIS that has been surgically treated or is planned for surgical treatment post-chemotherapy is allowed provided there is no evidence of further disease in the contralateral breast)
- Locally advanced breast cancer (T4 and/or N3 disease)
- Patients who have had breast conserving surgery in whom there is a contra-indication for, or refusal of post-operative radiotherapy
- Patients with positive surgical margins unless either
    - Deep surgical margin involvement following full thickness resection
    - Non-invasive cancer at surgical margins and a decision to perform mastectomy on completion of chemotherapy has already been made
- Patients not able or willing to give informed consent
- Patients known not to be available for a minimum of 5 years' follow-up
- Patients with known serious viral infection such as active Hepatitis B, Hepatitis C or HIV
- Patients with significant cardiac disease, such as impaired left ventricular function or active angina (requiring regular anti-anginal medication and/or resulting in restricted physical activity)
- Patients with a history of significant renal impairment or disease
- Simultaneous participation in the active intervention phase of another treatment trial
- Being approached and recruited into the active intervention phase of another treatment trial two months before or after recruitment into TACT2

RANDOMISATION PROCEDURE

ALL PATIENTS MUST BE RANDOMISED BEFORE CHEMOTHERAPY BEGINS

Sufficient time (e.g. 7 days) should be allowed for the patient to decide on trial entry, but the time which elapses between randomisation and start of chemotherapy should be minimised. It is recommended that patients considered for TACT2 are booked for their first chemotherapy treatment at the time of first referral.

An eligibility checklist and randomisation checklist should be completed prior to randomisation. To randomise a patient, simply telephone or fax your affiliated office:

Trials office	**Telephone**	**Fax**
TACT2 Trials Office at ICR-CTSU	020 8643 7150	020 8722 4368
CaCTUS, Edinburgh	0131 275 7276 or 0131 316 4278	0131 275 7512
Clinical Trials & Research Unit, Leeds	0113 343 6260	0113 343 1471
CR-UK Clinical Trials Unit, Birmingham	0121 414 3366 or 0121 414 7844	0800 328 6412

The person randomising the patient will then be asked to confirm that an eligibility checklist has been completed and to verify that the patient has signed the TACT2 consent form (this will be the subject of a later audit). They will also be asked for all the information on the randomisation checklist. A trial number and treatment allocation will be given over the phone and later confirmed in writing.

STUDY ORGANISATION

It is intended that TACT2 will randomise approximately 4400 patients, primarily from an estimated 100 centres in the UK. The aim is to complete accrual within 3 years if possible by maximising the number of UK centres and the speed with which they are activated.

Patient enrolment began in December 2005, the completion of enrolment is planned for late 2008 / early 2009 and completion of disease-free and survival status at 5 years is expected in early/mid 2013.

Several trials offices will undertake randomisation and data management. Each centre should agree its affiliation to one of the trials offices prior to participating in the study and enter all patients via the same trials office for the life of the trial. Data generated will be collected by the respective trials offices, who are responsible for checking incoming CRFs for compliance with the protocol, inconsistent and missing data, and for computerising data and resolving data queries. Data from all participating trials offices will be pooled and analysed at ICR-CTSU who have overall responsibility for all trial data, and for the ICR-CTSU SOPs that describe how the trial is to be conducted within participating trials offices. All data will be handled, computerised and stored in accordance with the Data Protection Act 1998. Quality control will be maintained through adherence to ICR-CTSU SOPs and through regular meetings of data management and statistical representatives from the participating trials offices.

TREATMENT PLAN - NON-INVESTIGATIONAL THERAPY

SURGERY

Patients may undergo breast conservation surgery with axillary clearance (preferably level III), or modified radical mastectomy, as per UK BASO guidelines. Patients undergoing sentinel node biopsy or a level 1 axillary sample MUST have either subsequent full axillary clearance or axillary radiotherapy if there is any evidence of nodal involvement by routine H&E staining. The date of surgery is the final date of surgery for malignancy, including re-excision, axillary clearance or mastectomy following initial breast conservation. If a sentinel lymph node biopsy or other sampling procedure is performed at initial surgery, and further axillary surgery is indicated due to detection of lymph node involvement, this may be carried out before randomisation (and date or surgery will be date of later axillary surgery) or alternatively after completion of chemotherapy. In this case any outstanding pathology data should be provided as soon as it is available. Reconstructive surgery conducted at the same time as surgery for malignancy is acceptable: in the event of a separate re-constructive or other surgical intervention (for example for flap necrosis), the date of surgery is the date of the previous intervention for malignant disease. Ideally, patients should be randomised into TACT2 within 4 weeks of surgery, but will be accepted into the trial up to 8 weeks from date of surgery for malignant disease.

ENDOCRINE THERAPY

Any previous HRT or pre-operative endocrine therapy is to be stopped at least 4 weeks prior to chemotherapy. All patients with ER and/or PgR positive tumours should commence treatment with tamoxifen 20mg daily for 5 years, within 4 weeks cessation of chemotherapy. In patients for whom tamoxifen is not appropriate (e.g. history of deep venous thrombosis, contravenes agreed local protocol), an aromatase inhibitor may be offered as an alternative. Aromatase inhibitors should only be used in accordance with local, regional or network policy, or for premenopausal women within the context of the SOFT study (vide infra).

LHRH analogue for ovarian protection in pre-menopausal women may be offered concurrently with chemotherapy, permitting concomitant recruitment into the NCRN OPTION trial. Pre-menopausal women who are still menstruating may be enrolled in the SOFT study, which randomises such patients between tamoxifen, ovarian ablation plus tamoxifen, and ovarian ablation plus exemestane, each for 5 years.

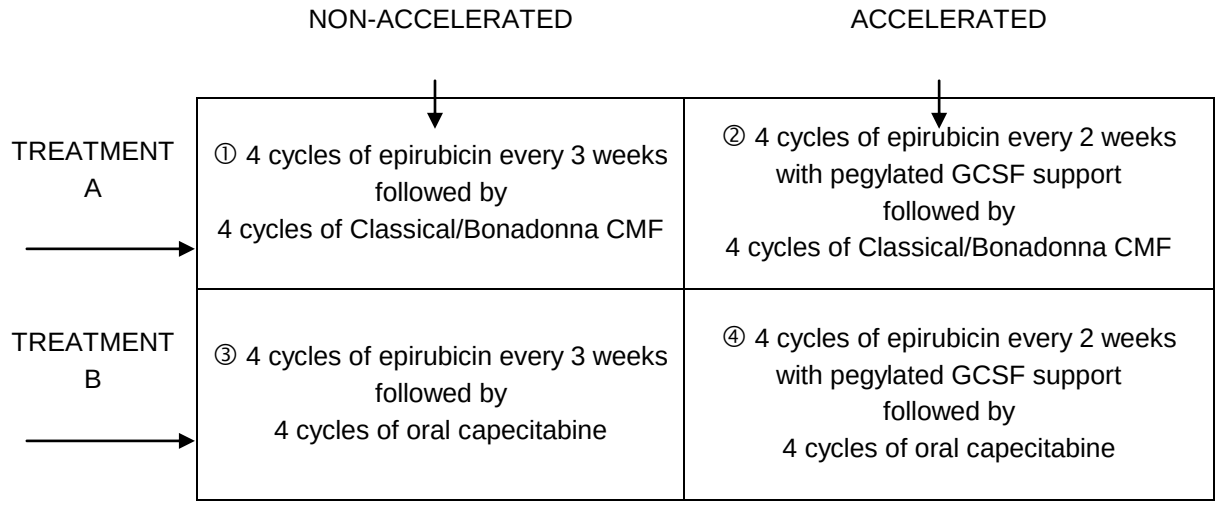
RADIOTHERAPY

Radiotherapy should be given, if required, after chemotherapy in keeping with local practice, and/or guidelines in Appendix 4.

TREATMENT PLAN - INVESTIGATIONAL THERAPY

CHEMOTHERAPY

Patients will be randomised into one of the four treatment arms (E-CMF; accelerated E-CMF; E-X; accelerated E-X) in a 1:1:1:1 ratio:



Doses:

Epirubicin 100 mg/m^2

Classical / Bonadonna CMF (on a 28 day cycle)

Cyclophosphamide	Either 100 mg/m^2 p.o. per day for 14 days or day 1 & 8 600 mg/m^2 i.v.
Methotrexate	40 mg/m^2 days 1 & 8
5-FU	600 mg/m^2 days 1 & 8

Capecitabine 2,500 mg/m^2 in divided doses for 14 days every 3 weeks

PEGYLATED GCSF

In the experimental accelerated arm, all patients should receive a single dose of 6mg pegylated-GCSF, (pegfilgrastim, Neulasta), on the day after the epirubicin as per the product license. In the event of safety and efficacy data becoming available that the drug is equally effective if given on the day of chemotherapy, then the protocol will be amended accordingly.

In treatment arms 1 and 3 the use of GCSF (preferably pegylated GCSF: see appendix 3) as secondary prophylaxis is encouraged following an episode of neutropenic sepsis or significant (>8 days) dose delay during cycle 1.

PRE-CHEMOTHERAPY INVESTIGATIONS

The following investigations are expected to be undertaken routinely before each cycle of chemotherapy in both treatment arms: symptom review, toxicity review, FBC, biochemical

profile (including liver function tests and serum creatinine and during capecitabine administration, calculated creatinine clearance).

Day 1 chemotherapy, and day 8 in the case of CMF, should only be administered if the neutrophil count >1.0 x 10^9/L and platelets >100 x 10^9/L.

SUPPORTIVE MEDICATION

Antiemetics

These may be given according to local practice. However, we recommend a 5HT3 antagonist (e.g. granisetron 3 mg i.v., or ondansetron 8 mg i.v.) and dexamethasone 8 mg i.v., before epirubicin, followed by domperidone 10-20 mg p.o. tds × 5 days, with dexamethasone 2 mg po tds x 3 days only.

H2-antagonists etc.

Ranitidine 150mg p.o. b.d. × 7 days, or similar, may be necessary to relieve steroid induced dyspepsia. Patients on regular cimetidine should be switched to another H2 receptor blocker or PPI as clinically appropriate prior to starting epirubicin in order to avoid the risk of increased epirubicin toxicity when used in conjunction with cimetidine.

Folinic acid rescue.

This is not routine in the use of CMF, but if it is a centre policy it is permitted provided it is given to all patients in CMF arms, and is not started until at least 24 hours after the CMF is administered.

Aperients

Aperients and/or glycerine suppositories will be occasionally required for relief or prophylaxis of granisetron-related constipation.

Prophylactic mouthwashes

Corsadyl mouthwash p.o. b.d is allowed throughout the period of anthracycline-containing chemotherapy.

Antibiotics

Prophylactic antibiotic therapy is not recommended.

DOSE MODIFICATIONS IN RESPONSE TO TOXICITY

Every effort must be made to deliver chemotherapy on schedule except where clinically a delay is indicated. In such circumstances, delays should be kept to a minimum, and clinicians should avoid the practice of automatically deferring by one week for minor haematological reasons: patients should be re-treated as soon as is clinically appropriate. The secondary prophylactic use of GCSF in the control arms (arms 1 and 3) after an episode of significant neutropenic delay is encouraged but not mandated.

Nadir full blood tests

Routine nadir blood counts are not required: dose modifications on the basis of nadir counts are specified for patients who have blood counts measured between treatments when experiencing significant toxicity.

Recommended Dose Modifications

Recommended dose modifications are specified separately for each component of the chemotherapy regimens.

Epirubicin

Patients experiencing nadir platelet counts ≤20 x 10^9/L, absolute neutrophil counts (ANC) < 0.25 x 10^9/L, neutropenic fever, or grades 3/4 non-haematological toxicity (e.g. mucositis) should have the subsequent day 1 dose of epirubicin reduced to 80% of previous dose. Day 1 chemotherapy should be delayed until platelet counts are ≥ 100 x 10^9/L, ANC ≥ 1.0 x 10^9/L, and non-haematological toxicities have recovered to ≤ CTC grade 1. If delay of a week or more is required, doses should be reduced to 80% of original.

Cardiac toxicity

This is not anticipated at the cumulative doses of epirubicin achieved in this protocol, namely 400mg/m^2 however, occasional patients with pre-existing cardiac pathology may develop problems, and clinicians should be alert to this possibility. In the event of congestive cardiac failure developing, patients should be investigated and treated as appropriate. If confirmed, epirubicin should be discontinued, and other chemotherapy may be given at the discretion of the investigator.

CMF

Patients experiencing nadir platelet counts ≤20 x 10^9/L, absolute neutrophil counts (ANC) < 0.25 x 10^9/L, neutropenic fever, or grades 3/4 non-haematological toxicity (e.g. mucositis) should have the subsequent day 1 doses of cyclophosphamide, methotrexate and 5-FU reduced to 80% of previous. Day 1 chemotherapy should be delayed until platelet counts are ≥ 100 x 10^9/L, ANC ≥ 1.0 x 10^9/L, and non-haematological toxicities (except alopecia) have recovered to ≤ CTCAE grade 1. If a delay of a week or more is required, doses should be reduced to 80% of original. In the event that on day 8 the platelet counts are < 100 x 10^9/L or ANC < 1.0 x 10^9/L, then that dose should be omitted, and the patient re-treated with day 1 of the next cycle being on the same date as originally planned.

CAPECITABINE

Patients should be carefully monitored for toxicity, particularly during the first cycle. All patients receiving capecitabine should be reviewed on day 8 of the first cycle in order to identify the very small proportion of patients with extreme sensitivity to 5-FU as a consequence of DPD deficiency. Such patients will also have problems with CMF and would be identified by the day 8 visit of their first CMF cycle. ANY patient experiencing ≥ grade 2 diarrhoea, mucositis or hand-foot syndrome (PPE, palms of the hands or soles of the feet tingle, become numb, painful, swollen, or red) by day 8 of their first cycle should stop their

capecitabine and discontinue study treatment. Toxicity due to capecitabine administration may be managed by symptomatic treatment, dose interruptions and adjustment of capecitabine dose. Once the dose has been reduced it should not be increased at a later time.

A maximum of two dose reductions are allowed per patient. capecitabine treatment interruptions are regarded as lost treatment days and the planned treatment schedule should be maintained. Patients who do not experience a recovery of the toxicity to grade < 1 after a maximum of 21 days delay (measured from the last planned treatment day) must discontinue study treatment.

The following rules will apply:

Grade 1:	Maintain dose level	
Grade 2/ 3:	1st episode	Interrupt until resolved to grade 0-1, then continue at 80% full dose
Grade 2/3:	2nd episode	Interrupt until resolved to grade 0-1, then continue at 64% full dose
Grade 2/3	3rd episode	Discontinue treatment permanently
Grade 4:	1st episode	Discontinue treatment permanently

Administration of capecitabine should be interrupted if treatment-related elevations in bilirubin of >3.0 x ULN or treatment-related elevations in hepatic aminotransferases (ALT, AST) of > 2.5 x ULN occur. Treatment should be resumed when bilirubin decreases to < 3.0 x ULN or hepatic aminotransferases decrease to < 2.5 ULN.

Neutropenia or thrombocytopenia

In case of neutropenia (neutrophils <1 x10^9/L) or thrombocytopenia (platelets < 100x10^9/L) on the planned treatment day, the treatment should be delayed until recovery of neutrophils (neutrophils >1 x 10 9/L) and/or platelets (platelets >100 x10^9/L) for a maximum of 21 days.

- In case of a first episode of hematological non-recovery (neutrophils <1 x10^9/L or platelets <100 x10^9/L) on the planned start day of a new cycle, the treatment should be delayed until recovery of neutrophils (neutrophils ≥1 x10^9/L) and/or platelets (platelets ≥100 x10^9/L) up to a maximum of 21 days. Subsequent doses should be given at 80%.

- In case of a second episode of hematological non-recovery on the planned start day of a new cycle, the treatment should be delayed until recovery of neutrophils and/or platelets up to a maximum of 21 days. All subsequent doses should be reduced again by 20% to 64% of the initial dose.

- Patients whose counts do not recover after a maximum treatment delay of 21 days (from the planned day of drug delivery) and patients who present a third episode of haematological non-recovery must discontinue study treatment .

It is not anticipated that capecitabine at the dose of 2,500 mg/m^2 in divided doses for 14 days every 3 weeks will cause significant myelosuppression. However in the case of febrile neutropenia or life threatening infection, any further drug delivery should be discontinued for the remainder of that cycle and until full recovery. If on the planned start day of a new cycle, a patient has febrile neutropenia, the next cycle should be delayed until complete resolution. A maximum of 15 days delay is allowed. Doses in all subsequent cycles should be reduced by 20% after a first episode, and by a further 20% (36% of the starting dose) after a second episode. Patients who have febrile neutropenia after a 36% dose reduction should discontinue.

Renal function

It is well recognised that in patients with impaired renal function capecitabine can cause increased toxicity. Therefore, not withstanding the above rules for dosing in the face of toxicity, any patient whose calculated creatinine clearance drops below 50 ml/min should have the dose of capecitabine reduced to 75% of the dose of the previous cycle. If the calculated creatinine clearance falls below 40 ml/min, then they cannot be treated with capecitabine, and if there is no recovery within 21 days of a cycle being due, they must come off study treatment.

DRUG SUPPLIES & LABELLING

Capecitabine (Xeloda®) is supplied free of charge by Roche. Neulasta is supplied by Amgen at a discounted rate. Further details on costing are given in Appendix 3. Guidelines for ordering Xeloda and Neulasta, and drug labelling requirements are contained within the Trial Guidance Notes.

PHARMACOVIGILANCE

DEFINITIONS

Serious Adverse Events (SAEs)

Serious adverse events are those that occur during or within 30 days of administering randomised treatment, whether or not it is related to the randomised treatment. ICH GCP defines an SAE as any untoward medical occurrence shown in Box 1:

BOX 1

- Results in death
- Is life-threatening*****
- Requires in-patient hospitalisation****** or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in offspring of patient regardless of time to diagnosis).
- Is an important medical event (an event that jeopardizes the patient or may require intervention to prevent one of the other outcomes listed above.

***** *The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.*

****** *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.*

For the TACT2 trial, other important medical events that may not result in death, are not life threatening, or do not require hospitalisation may be considered a serious adverse events when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in Box 1.

Serious Adverse Reactions (SARs)

SARs are those SAEs which are considered to be possibly / probably / definitely related to the trial treatment. Most SARs can be classified as "expected".

Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARs are SARs which are not classified as "expected". SUSARs require expedited reporting by the trial sponsor (i.e. Chief Investigator with ICR-CTSU) to MHRA, therefore every effort should be made to notify ICR-CTSU within the timeframe shown below.

RECORDING & REPORTING OF SAEs

SARs shown in Box 2 do not require immediate reporting using an SAE Report Form, but should be reported using a SAR form which provides data required for annual line listings to the MHRA. All other SAEs (except those shown in box 3) should be reported within 24 hours of the investigator becoming aware of it, by completing an SAE Report Form and faxing it to:

ICR-CTSU
Section of Clinical Trials, Institute of Cancer Research, Sutton
FAX No: 020 8722 4368

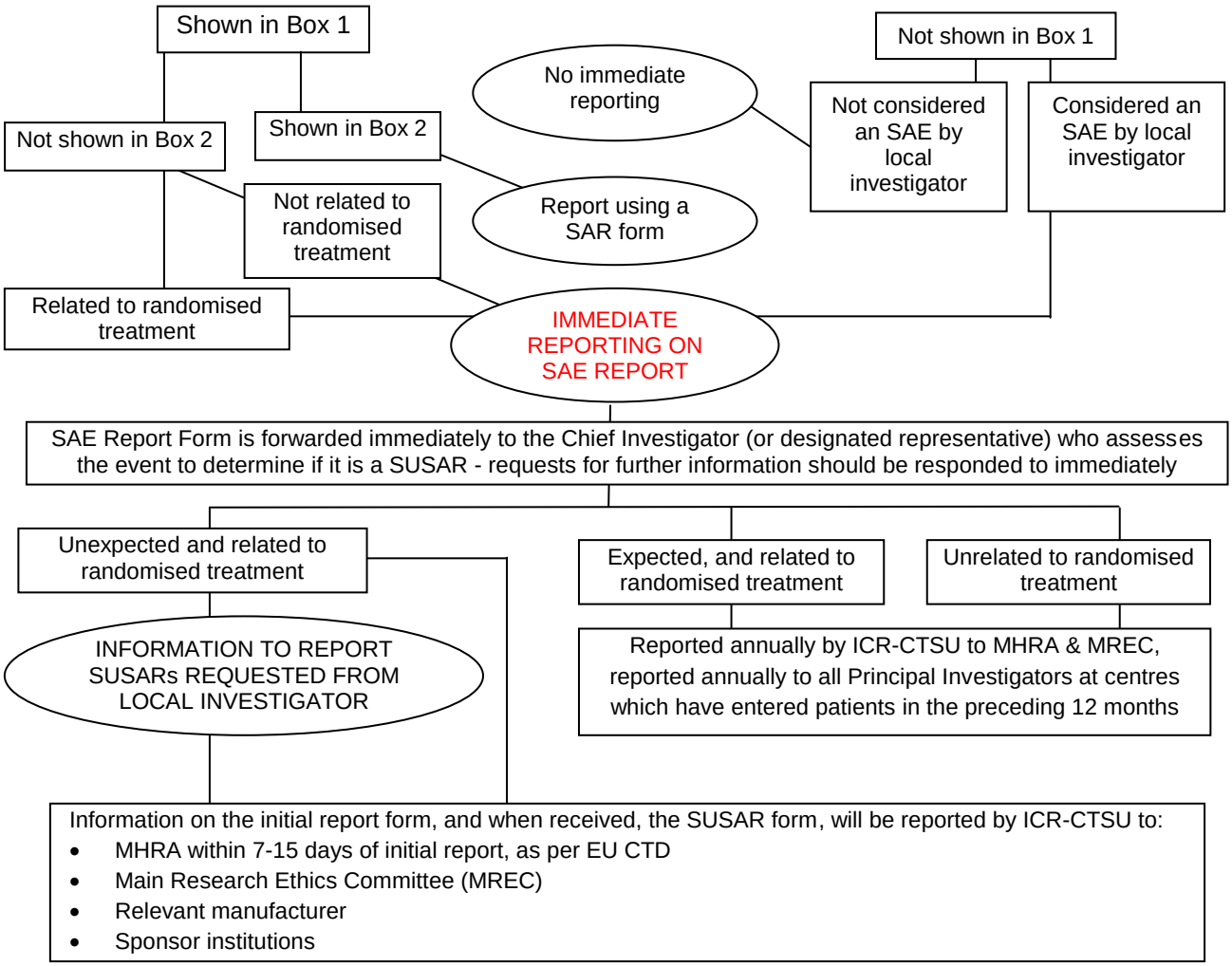
<table>
<tr><th colspan="2">BOX 2
SARs occurring within 30 days of receiving trial therapy that should be reported using a SAR form:</th><th>BOX 3
SAEs that do not require immediate reporting using a faxed SAE form:</th></tr>
<tr><td>Epirubicin, Neulasta, Cyclophosphamide, Methotrexate, 5FU

Hospitalisation due to:
Neutropenia
Febrile neutropenia
Diarrhoea
Infections, including those to Hickman line, catheter or wound
Pyrexia
Sore throat
Nausea or vomiting
Cellulitis</td><td>Capecitabine

Hospitalisation due to:
Infections, without grade 3 or 4 neutropenia, including those to Hickman line, catheter or wound
Pyrexia
Sore throat
Nausea or vomiting
Cellulitis</td><td>Any trial drug

Hospitalisation or death due to disease progression
Hospitalisation for study drug administration, palliative care, terminal care or elective surgery</td></tr>
<tr><td colspan="3">NB – All hospitalisations, relapses and deaths <u>MUST</u> be reported on the CRFs</td></tr>
</table>

Flow diagram of which SAEs require immediate reporting, and action taken following the report



FOLLOW-UP OF SARs, SAEs & SUSARs

The subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until disease has stabilised. Information on final diagnosis and outcome of SARs/SAEs which may not be available at the time the SAR/SAE is initially reported should be forwarded on the SAR/SAE Report Form, as soon as this information is available. Follow-up may continue after completion of protocol treatment if necessary. Any SAE occurring whilst the patient is receiving capecitabine will be passed to Roche. If there is any information that Roche are legally required to collect which has not been captured on the SAE Report Form, the information will be requested. All information regarding an SAE should be faxed to the ICR-CTSU, and information required by drug manufacturers will be passed on by that office. Centres are free to volunteer information to drug manufacturers if they wish, but are under no obligation to do so.

OTHER TOXICITY REPORTING

Any relevant information on SAEs that are shown in Box 1 and also Box 2 will be collected for the whole trial population on the 'NHS Resource Usage form' which is to be completed for all patients at all cycles of chemotherapy.

It is not possible to compare the relative de-merits of chronic low-level toxicities (e.g. grade 1 or 2 hand-foot syndrome) with high-grade acute toxicities. Therefore detailed toxicity reporting on all patients as a discriminator between the chemotherapy treatment arms is of little value in the absence of Quality Of Life measures to assess the global impact upon each patient. Thus detailed clinically assessed toxicity will only be collected via CRFs for those patients entered from centres participating in the Quality Of Life (QL) sub-study (appendix 1). A similar approach to limited recording of detailed toxicity was taken in the CALGB 9741 trial of accelerated chemotherapy.

PATHOLOGY REPORTING

Standard information will be collected on all patients from the local histopathology report. This will include data regarding pathological size, tumour grade, ER status (and actual Allred score/ percentage of +ve cells if available), and the total number of axillary lymph nodes removed, and the number that contain metastatic deposits. In addition, we will record PGR status, and HER2 status where available.

TRIAL EVALUATIONS

Case record forms (CRFs) are listed below. Further details on how and when to complete CRFs and to whom they should be returned are in the Standard Operating Procedures (SOPs). The Trial Management Group reserve the right to amend or add to the CRFs as appropriate. Such changes do not constitute a protocol amendment, and revised or additional forms should be used by centres with immediate effect.

At baseline:

- Eligibility checklist
- Randomisation form
- Baseline form
- Normal Activity form

At the end of each cycle of chemotherapy:

- Chemotherapy Treatment form
- NHS Resource Usage form
- Toxicity form (for centres participating in the QL and Toxicity sub-study)

At the end of radiotherapy (or end of chemotherapy if none is given):

- Adjuvant Treatment form

At 12, 18 and 24 months from randomisation, and annually thereafter:

- Follow-up forms
- Ovarian Function form (pre-menopausal patients only, at 12 months after chemotherapy)

As appropriate:

- Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR) Forms

- Deviation form
- Transfer form
- Recurrence and second primary breast cancer forms
- Death form

SCHEMA OF TRIAL EVALUATIONS

Form	At baseline	chemotherapy cycles 1-8			After RT	12 months	18 months	24 months	annually thereafter
		D1	during	end					
Eligibility checklist	X								
Randomisation checklist	X								
Baseline form	X								
Normal Activity form**	X								
Chemotherapy form		X	*						
NHS resource usage form **				X		X	X	X	X
Toxicity form (for centres participating in the Toxicity sub-study below)				X					
Adjuvant treatment					X				
Follow-up forms						X	X	X	X
Ovarian Function (if required)							X		
Recurrence, second primary & death forms (if required)		X	X	X	X	X	X	X	X
SAE/SAR forms (if required)		X	X	X					
Deviation forms (if required)		X	X	X	X	X	X	X	X
Transfer forms (if required)		X	X	X	X	X	X	X	X

* Patients receiving capecitabine should additionally be seen on day 8 of their first cycle of capecitabine

**these forms to not contain medical information, and source data in patient notes is not required

Patients should be followed-up as per local practice for patients entered into trials in early breast cancer, but the minimum must include 6-monthly clinic visits for toxicity assessments and clinical examination until the end of year 2 and then annual thereafter (to correspond with the follow-up forms). Annual follow-up data will be collected for as long as the Trial Management Group consider it is contributing to the research question. The information required will include sites of recurrence, date of recurrence, vital status, and date and cause of death. Should a patient be discharged to GP care or another hospital, all reasonable attempts should be made by the randomising hospital to collect follow up information from these sources and send it to their affiliated trials office at the prescribed time points laid down in the Trial Guidance Notes. When electronic methods of routine data collection are considered to be reliable and complete, data will continue to be collected via these methods, subject to the approvals required by the "custodian" of that routine data.

Should the GP or other hospital be unable to provide information, the Trials Office should be informed. The Trials Office will then apply to a national records office to either trace the patients' new GP *or* give notification in the event of their death.

Information on second primary breast cancers and other second primary tumours will also be recorded. Regular (annual or bi-annual) imaging of the breasts (e.g. mammography or MRI) should be part of the follow-up protocol for a minimum of 10 years according to local practice.

Long term follow up

Changes of Principal Investigator after the end of the intervention phase of the trial (i.e. when all patients have completed study drug) do not need to be notified to the regulatory authority or the responsible Research Ethics Committee. However, the affiliated Trials Office should be notified of any changes of PI and the local Research and Development office at the Institute of the PI should be informed.

Relapse

Recording of relapses will be done as for TACT. The date of relapse is taken as the date of first confirmed recurrence by an appropriate investigation such as cytology, histology, or imaging wherever possible. In the absence of such confirmation, the date of first clinical suspicion will be taken provided that suspicion leads to a change or re-introduction of anti-cancer therapy. The management of recurrence will be at the discretion of the clinician. Follow up information should continue to be provided until the patient dies. Relapses do not require immediate reporting, and should be recorded on the next due follow up form.

Quality of Life (Appendix 1)

A sub-study addressing quality of life (QL) will be assessed in a cohort of 1000 patients, who will also be assessed for detailed toxicity. The frequency of adverse events and toxicity will be assessed after 800 patients have been entered into the QL study and the planned total of 1000 patients will be adjusted accordingly to allow statistical discrimination between the 4 arms.

Cost and Resource Use *(Appendix 3)*

This assessment will allow for calculations of cost and resource use for adjuvant chemotherapy, and for a comparison between the four different chemotherapy treatments.

STATISTICAL CONSIDERATIONS

STRATIFICATION

Randomisation will be stratified by:

- Centre
- Nodal status: [Node negative, Node positive],
- Indication for endocrine therapy (Yes / No)
- Age: ≤50; >50 years.

Baseline prognostic information on number of nodes involved, grade, ER status, PgR status, HER2 status (where available) and tumour size and radiotherapy usage will be recorded and analyses adjusted for these factors will be conducted as appropriate.

RANDOMISATION

Randomisation will be conducted according to variable sized permuted blocks.

SAMPLE SIZE

The trial will have a 2 x 2 factorial design. The type of hypothesis under investigation is different for the two treatment questions hence the justification of patient numbers and resulting power of the trial is specific to each question. It is assumed that the 5 year DFS in the standard E-CMF arm will be 80%.

i) comparison of standard vs accelerated treatment – the trial aims to detect an improvement in DFS associated with the accelerated schedule

3876 patients will be required to detect a 4% difference (HR=0.78) between the schedules with 90% power and alpha=0.05 (2 sided).

ii) **comparison of E-CMF vs E-X – the trial aims to exclude inferiority of E-X compared with E-CMF**

Evidence from advanced disease suggests that substituting X (Xeloda) for CMF should result in equivalence of E-X and E-CMF, however E-X will be considered a viable alternative if it can be demonstrated that it is not more than 3% worse than E-CMF. A total of 4400 patients will provide 80% chance that the lower 90% confidence limit for the difference between the E-X and E-CMF schedules will exclude 3% if the arms are truly equivalent.

The target accrual is therefore 4400 patients. It is intended that patients will be randomised into both components of the trial, however if centres are unable to accommodate accelerated treatment schedules then they may be permitted to enter only the E-X versus E-CMF comparison.

ANALYSIS PLAN

The analysis of overall survival and disease-free survival will be from the time of randomisation to the date of death or relapse, respectively, or the censor date (date last seen alive/death from other causes). Disease-free survival is taken as the time from trial entry to the date of first confirmed recurrence of this breast cancer. New primary breast cancer within either breast is not considered a relapse, but will still require reporting on follow-up forms. Treatment comparisons will be tested with and without adjustment for the stratification and baseline prognostic factors as above.

Analyses will be based on the intention to treat principle. For the comparison between standard and accelerated schedules the principal analysis will be a logrank comparison of schedules ① and ③ versus schedules ② and ④. For the comparison of E-X with E-CMF a 90% confidence interval for the difference between schedules ① and ② compared with schedules ③ and ④. In both cases Cox regression methods will be used for multivariate

analyses (to further adjust for clinical factors likely to influence prognosis) and to estimate the hazard ratio and its associated confidence intervals and to test for interactions between the schedules. Probabilities of DFS and OS will be presented as Kaplan-Meier survival curves with fixed term survival estimates. Baseline characteristics will be described by randomised treatment group. Comparisons will be performed using simple parametric, non-parametric or chi-squared tests as appropriate. Tests will be two-sided and 95% confidence intervals will be used. Heterogeneity of effects by centre will be investigated.

Toxicity and the frequency and nature of adverse events will be compared between the randomised groups. Summary measures, non-parametric tests as well as analyses incorporating respected measures will be used as necessary. In particular, the proportion of patients experiencing toxicity of CTCAE grade 3 or 4 and the maximum CTCAE toxicity grade will be compared. An investigation of treatment compliance with randomised treatment will be based on frequency of dose reductions and delays. Association will be investigated between observed toxicity and patients' co-morbidity.

INTERIM ANALYSES & ROLE OF THE DATA MONITORING & ETHICS COMMITTEE (DMEC)

A DMEC will be set up to monitor the progress of the trial. The committee members will meet in confidence at regular intervals as they see fit but at least annually. Following each meeting they will produce a report of their findings and recommendations. This report will be submitted to the Trial Management Group and Trial Steering Committee, the main REC and the MHRA, as required.

Interim analysis of side effects, tolerability, disease-free and overall survival for all randomised patients will be performed at approximately yearly intervals. These analyses will be supplied in strict confidence by the trial statistician to the DMEC together with any other analyses that the DMEC may request. In particular, the DMEC will be asked to review emerging data from both randomised comparisons. If evidence emerges from this or other trials that it is no longer ethical to continue randomising patients into one or other randomisation, a change in the design of the trial to reflect this will be considered. No results on survival or recurrence will be made available to investigators or any other party until at least two years after the last patient is entered unless the DMEC determines that it would be unethical to withhold the interim results. Summary data on side effects and compliance will be circulated to investigators every six months. Specific consideration will be given to early toxicity and compliance and also later to any evidence of an interaction between schedules that would negate the appropriateness of the 2 x 2 design and require a consequential increase in patient numbers.

Detailed analysis and publication of the QL and toxicity sub-study may be considered before the primary end-point is reached, but only with the agreement of the Trial Management and Steering Groups.

The main criterion for early stopping of the trial by the Trial Steering Committee upon suggestion from the DMEC and request from the Trial Management Group will be that

evidence from the trial and from other sources suggests a) proof beyond reasonable doubt that for all, or for some types of patient, one treatment regimen is clearly indicated or contra-indicated in terms of a net difference in DFS or OS, and b) evidence that might reasonably be expected to influence routine clinical practice. Criteria for the above will usually be a difference in DFS or OS at any stage significant at $p < 0.001$ by overall log-rank analysis. Use of the Haybittle- Peto interim stopping criteria will not materially affect the overall alpha in the final analysis.

The DMEC will however reserve the right to release any data on outcome or side-effects through the Trial Steering Committee to the Trial Management Group (and if appropriate to participants) if it determines at any stage that the combined evidence from this and other studies justifies it.

MILESTONES

The recruitment rate will be between 1000 - 1350 patients per annum. Assuming an optimistic recruitment of 1350 per annum, then 4500 patients will be recruited at the end of the first 3 years. Patient enrolment began in December 2005, the completion of enrolment is planned for late 2008 /early 2009, and completion of relapse-free and survival status at 5 years is expected in early/mid 2013. The milestones assume projected event rates that may alter depending on the patient population recruited.

COMPLETION OF THE STUDY & DEFINITION OF STUDY END DATE

For the purposes of Clinical Trial Authorisation (CTA) and for Research Ethics Committee approval, the study end date is deemed to be the date of last data capture

Annual follow-up data will be collected for as long as the Trial Management Group consider it is contributing to the research question.

.

PREDICTIVE MARKER STUDIES

Detailed histopathological studies on tumour tissue will allow for potential analyses addressing the importance of conventional pathological factors (especially ER and PGR status), as well as a number of newer candidate predictive markers, using both conventional multivariate techniques, as well as neural network analysis. Similarly there is a pharmacogenomic study, with peripheral blood samples to be collected from all (consenting) patients. This will look at DNA polymorphisms in the genes responsible for metabolising the drugs administered, and link these to pharmacokinetic data in the subgroup of patients enrolled in that study, and to the toxicity and outcome in all patients.

COMPATIBILITY WITH OTHER STUDIES

The TACT2 Trial Management Group consider that patients may also be enrolled in the SOFT, SUPREMO, OPTION, REACT, IMPORT High, ALLTO, POETIC, MAPLE and Lapatinib Presurgery studies, providing of course they meet the inclusion criteria of these other studies. Patients who have had short duration (up to 28 days) pre-operative endocrine

treatment may also be enrolled, provided it is either given out with a study, or if within a study, without therapeutic intent. Compatibility with other studies that may open during the time that this trial enrols patients will be considered on a case by case basis by the Trial Steering Group, and in the light of the prevailing view of the MREC on compatibility (vide supra for relevant exclusion criteria).

RESEARCH GOVERNANCE

TRIAL ADMINISTRATION & LOGISTICS

Lothian Health Board and The Institute of Cancer Research are co-sponsors of the TACT2 Trial. Sponsorship activities and delegated responsibilities are shared between Lothian Health Board, the employer of the Chief Investigator; and The Institute of Cancer Research, in accordance with The Medicines for Human Use (Clinical Trials) Regulations 2004 and in line with the Research Governance Framework for Health and Social Care and ICH GCP. Both parties agree to allow inspection of sponsors' premises by the competent authorities.

Lothian Health Board has sponsorship responsibility for obtaining authorisation and appropriate ethics committee opinion (Part 3 of the Regulations) and for Pharmacovigilance (Part 5 of the Regulations). The following responsibilities have been delegated:

A to The Institute of Cancer Research:

1. Request clinical trial authorisation, amend the request;
2. Ensure an appropriate ethics opinion has been sought, and any amendments have been approved;
3. Give notice of amendments to CTA or protocol, make representations about amendments to the licensing authority;
4. Give notice a trial has ended;
5. Keep records of all serious adverse events reported by investigators;
6. Ensure recording and prompt reporting of serious adverse reactions to the Chief Investigator;
7. Report to the MHRA any serious adverse events which the chief investigator considers to be SUSARs;
8. Ensure investigators are informed of SUSARs;
9. Ensure all SUSARs including those in third countries entered into European database;
10. Provide annual list of SUSARs and a safety report.

The following responsibilities are retained by the Chief Investigator, or delegated in his absence, a named deputy:

11. Prompt decision as to which serious adverse events are SUSARs, and prompt reporting of that decision to the Section of Clinical Trials, ICR-CTSU, The Institute of Cancer Research for onward reporting to the licensing authority and Sponsoring Institutions.

B delegated to participating centres:

1. Ensure recording and prompt reporting of suspected unexpected serious adverse reactions (SUSARs) – delegated to participating centres;

The Institute of Cancer Research has responsibility for ensuring the research is conducted in accordance with Good Clinical Practice (Part 4 of the Regulations). The following responsibilities have been delegated:

A to Lothian Health Board:

2. Take appropriate urgent safety measures – delegated to the Chief Investigator, Lothian Health Board.

B delegated to participating centres:

1. Put and keep in place arrangements to adhere to the principles of GCP;
2. Keep a copy of all 'essential documents' (as defined under ICH GCP) and ensure appropriate archiving and destruction of documentation once the study has ended;
3. Ensure IMPs (investigational medicinal products) are made available to subjects free of charge;
4. Take appropriate urgent safety measures

Responsibilities are defined in an agreement between an individual participating centre and The Institute of Cancer Research.

The Institute of Cancer Research is responsible for administering funding and co-ordinating any required legal agreements and investigator statements.

The delegation of sponsorship responsibilities does not impact on or alter standard NHS indemnity cover. The agreement of delegated responsibilities is viewed as a partnership and as such it is necessary to share pertinent information between The Institute of Cancer Research and Lothian Health Board/Chief Investigator, including proposed inspections by the MHRA and/or other regulatory bodies.

PROTOCOL COMPLIANCE & MONITORING

TACT2 is being conducted in accordance with the professional and regulatory standards required for non-commercial research in the NHS under the EU Directive. Before activating the trial, participating centres are required to sign an agreement accepting sponsorship responsibility for all trial activity which takes place within their centre as stated in the Trial Administration and Logistics section above.

Staff from centres that have attended the Investigator Launch meeting will not require start-up visits unless they are requested by the Trials Unit or Principle Investigator.

DATA ACQUISTION & ON-SITE MONITORING/AUDITING

Trials Unit staff may visit centres to confirm that agreements are being adhered to, specifically to carry out source data verification and confirm compliance with the protocol and the protection of patients' rights as detailed in the Declaration of Helsinki. Copies of the Declaration may be obtained from the designated Trials Unit. By participating in the TACT2 trial the Principal Investigators at each centre are confirming agreement with his / her local NHS Trust to ensure that:

- sufficient data is recorded for all participating patients to enable accurate linkage between hospital records and CRFs
- source data and all trial related documentation are accurate, complete, maintained and accessible for monitoring and audit visits
- all staff at their centre who are involved with the trial will meet the requirements of the EU Directive
- original consent forms are dated and signed by both patient and investigator and are kept together in a central log together with a copy of the specific patient information sheet(s) given at the time of consent
- copies of CRF's are retained for 15 years to comply with international regulations
- staff will comply with the Standard Operating Procedures for TACT2

The affiliated Trials Unit will monitor receipt of CRFs and evaluate incoming CRFs for compliance with the protocol, inconsistencies and missing data.

Participating centres may be monitored by the Trials Unit and possibly by Health Authorities. Monitoring by Trials Units will confirm compliance with the protocol and source data verification (SDV).

Site auditing/monitoring will be conducted at a proportion of participating centres at least once during the course of the trial. If a monitoring visit is required the Trials Unit will contact the centre to discuss dates of proposed visit. Once a date has been confirmed a list of names of patients whose notes will be monitored / audited during the visit will be sent to the centre. This list will be sent out in advance to give sufficient time for the notes to be made available. (The Trial Statistician will decide the percentage of patients to be monitored / audited).

If any problems are detected in the course of the monitoring / auditing visits then the Principal Investigator and the Trials Unit will work together to resolve queries to determine the centre's future participation in the study.

ARCHIVING

All source and study documentation must be securely retained by the Principal Investigator for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications. Source data (including data on any patients who die) must be retained for the duration of the recruitment, treatment and follow up phases of the trial for inspection by representatives of ICR-CTSU or affiliated trials office, where these are different.

FINANCIAL MATTERS

The trial is investigator designed and led, and has been approved by CTAAC. It is endorsed by Cancer Research UK and meets the criteria for R&D support as outlined in the Statement of Partnership on Non-Commercial R&D in the NHS in England.

Research costs (to the clinical trials offices) are being funded by Cancer Research UK with additional funding in the form of educational grants provided by Roche, Amgen and Pfizer. If additional financial support is received from any other source, this will be made apparent to the approving MREC and CTAAC, but will not require a protocol amendment.

No individual per patient payment will be made to trusts or investigators, but NCRN (or regional equivalent) network resources should be made available as the trial is part of the NCRI portfolio by virtue of its approval by CTAAC.

CLINICAL RISK ASSESSMENT

Generic Risk Assessment Hazards to patients, study and organisation have been performed for TACT2 and have been considered low risk.

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 Trial Management Group, representatives of the regional trials groups, and high accruing clinicians. The trials offices and all participating centres and clinicians will be acknowledged in this publication. All presentations and publications relating to the trial must be authorised by the Steering Group. There will hopefully be secondary publications relating to the detailed toxicity and Quality of Life study, and the various biological studies. The authorship on these secondary publications will reflect the intellectual and time input into these studies, and will not be the same as on the primary publication. No investigator may present or attempt to publish data relating to TACT 2 without prior permission from the Trial Management Group.

CONFIDENTIALITY & LIABILITY

LIABILITY / INDEMNITY / INSURANCE

This study is an investigator-led trial endorsed by the Clinical Trials Awards and Advisory Committee (CTAAC) of Cancer Research UK and the UK Medical Research Council. Indemnity for participating hospitals is provided by the usual NHS indemnity arrangements.

PATIENT CONFIDENTIALITY

The patient's full name, date of birth, hospital number and NHS number (CHI number in Scotland) will be collected at randomisation to allow tracing through national records and to assist with long term follow-up. The personal data recorded on all documents will be

regarded as confidential, and to preserve each subject's anonymity, only their initials and date of birth will be recorded on subsequent Case Report Forms.

The investigator must keep a separate log of patients' trial numbers, names, addresses and hospital numbers. The investigator must maintain in strict confidence trial documents, which are to be held in the local hospital (e.g. patients' written consent forms). The investigator must ensure the patient's confidentiality is maintained.

ICR-CTSU and all other participating trials offices will maintain the confidentiality of all subject data and will not reproduce or disclose any information by which subjects could be identified, other than reporting of serious adverse events. Representatives of the trials offices will be required to have access to patient notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times. (In the case of special problems and / or government queries, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected).

ETHICAL CONSIDERATIONS

The study has been approved by MREC for Scotland. Before entering patients, the Principal Investigator at each site is responsible for gaining Site Specific Assessment and advising the main REC. Patients should be asked to sign the main consent form and the consent form for the biological studies after having both verbal and written information. Patients who do not wish to take part in one or either of the biological studies may take part in the main trial. Patients participating in the Quality of Life Study must also sign the Quality of Life consent form. All consent forms must be countersigned by the Principal Investigator or a designated individual, and a record of who designated individuals are and the circumstances under which they countersign consent forms must be clearly documented at the research site and be available for inspection together with original copies of all signed patient consent forms.

The TACT2 patient information sheet should be provided in addition to the standard chemotherapy patient information sheets that are provided by the centre and used in routine practice.

WITHDRAWAL OF PATIENTS FROM STUDY TREATMENT

Patients who do not receive their allocated treatment for any reason should be treated at the discretion of their clinician. However, analyses of all outcome data will be on the basis of intention to treat. Unless the patient requests otherwise, all CRFs, including long term follow up, should be completed, regardless of treatment actually received. A trial deviation form should be completed to record details of deviation from treatment allocation, and also for any patient who withdraws consent for further follow up. Patients are asked prior to randomisation to consent to follow up should they withdraw from the treatment allocation (see patient information sheet and consent form), and any patient unwilling to give that assurance prior to trial entry should not be randomised. Patients are, however, free to reverse that decision at any time without giving a reason.

REFERENCES

1. CRUK, Cancer Statistics. www.cancerresearchuk.org, 2003.
2. Hudis, C., New approaches to adjuvant chemotherapy for breast cancer. Pharmacotherapy, 1996. 16(3 Pt 2): p. 88S-93S.
3. Irvin, R.J. and J.G. Kuhn, Financial considerations in the use of adjuvant chemotherapy. Cancer Treat Res, 1992. 60: p. 207-22.
4. Bishop, J.F. and K. Macarounas-Kirchman, The pharmacoeconomics of cancer therapies. Semin Oncol, 1997. 24(6 Suppl 19): p. S19-106-S19-111.
5. Annemans, L., et al., Cost-Effectiveness of the Sequential Addition of Taxol (T) to Doxorubicin Plus Cyclophosphamide (AC) in the Adjuvant Chemotherapy of Patients with Node-Positive Breast Cancer. ASCO Proc, 2000. 19: p. 1752A.
6. Brinkley, D. & J.L. Haybrittle, The curability of breast cancer. Lancet, 1975. 2(7925): p. 95-7.
7. Adair, F., et al., Long-term follow-up of breast cancer patients: the 30-year report. Cancer, 1974. 33(4): p. 1145-50.
8. Schabel, F., Concepts for the successful treatment of micrometastases. Cancer, 1975. 35: p. 15-24.
9. Fisher, B., Surgical adjuvant therapy for breast cancer. Cancer, 1972. 30(6): p. 1556-64.
10. EBCTCG, Polychemotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet, 1998. 352(9132): p. 930-42.
11. Levine, M.N., Bramwell VH, Pritchard KI, et al., Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol, 1998. 16(8): p. 2651-8.
12. Bonneterre, J. Roché H, Bremand P et al., Results of a randomized trial of adjuvant chemotherapy with FEC 100 in high risk node-positive breast cancer patients. French Adjuvant Study group (FASG) ASCO Proc, 1998. 17: p 473A
13. Poole CJ., Dunn JA., et al., NEAT (National Epirubicin Adjuvant Trial) and SCTBG BR9601 (Scottish Cancer Triaols Breast Group) phase III adjuvant breast trial shows a significant relapse-free and overall survival advantage for sequential ECMF (abstract). ASCO Proc, 2003 22:4
14. Wunderlich, A K and Schmalenberg, H S. Practicability and acute haematological toxicity of 2- and 3-weekly CHOP and CHOEP chemotherapy for aggressive non-Hodgkin's lymphoma: results from the NHL-B trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL) Ann Oncol 2003;14:881-893
15. Woll, P J, Thatcher, N, Lomax, L, Hodgetts, J, Lee, S M, Burt, P A, Stout, R, Simms, T, Davies, R, Pettengell, R, Thatcher, N, Girling, D J, Hopwood, P, Sambrook, R J, Qian, W, Stephens, and RJ. Use of hematopoietic progenitors in whole blood to support dose-dense chemotherapy: a randomized phase II trial in small-cell lung cancer patients Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party J Clin Oncol 2001;19:712-719
16. Huisman, C, Biesma, B, Postmus, P E, Giaccone, G, Schramel, F M, Smit, E F, Woll, P J, Thatcher, N, Lomax, L, Hodgetts, J, Lee, S M, Burt, P A, Stout, R, Simms, T, Davies, R, Pettengell, R, Thatcher, N, Girling, D J, Hopwood, P, Sambrook, R J, Qian, W, Stephens, and RJ. Accelerated cisplatin and high-dose epirubicin with G-CSF support in patients with relapsed non-small-cell lung cancer: feasibility and efficacy Use of hematopoietic progenitors in whole blood to support dose-dense chemotherapy: a randomized phase II trial in small-cell lung cancer patients Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity

of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party Br J Cancer 2001;85:1456-1461
17. Citron ML., Berry DA., Cirrincione C., et al., Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003 21:1431-9.
18. Oshaughnessy, J A, Blum, J, Moiseyenko, V, Jones, S E, Miles, D, Bell, D, Rosso, R, Mauriac, L, Osterwalder, B, Burger, H U, and Laws, S. Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer Ann Oncol 2001;12:1247-1254
19. Blum, J J, Buzdar, A U, LoRusso, P M, Kuter, I, Vogel, C, Burger, H U, Brown, C, and Griffin, T. A multicenter phase II trial of Xeloda (capecitabine) in paclitaxel-refractory metastatic breast cancer (MBC) Proc ASCO 1998;17:125-(abstr 476)
20. Toi, M and Ohno, S. The role of thymidine phosphorylase (TP) in choosing FU/capecitabine chemotherapy Proc ASCO 2003;22:34-abstract No 137

21. Hudis, C, Barlow, W, Costantino, J, Gray, R, Pritchard, K, Chapman, JA, Sparano, J, Hunsberger, S, Enos, R, Gelber, D, Zujewski, JA. Proposal for Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials: The STEEP System. J Clin Oncol 2007 25:2127-2132.

APPENDIX 1 Sub-study 1: Quality of Life & Toxicity

Reasons for stopping recruitment and planning to open a new QL study

The QL Study as previously planned was challenging to manage because of the critical time points of the follow up postal questionnaire booklets sent out by the QL coordinator, in particular the on-treatment 1st phase (6 weeks) and the end of treatment 1st phase (8-12 weeks in accelerated and standard arm respectively). The fast recruitment into the main study and QL study added additional challenges, increasing the intensity and volume of work. As a result we found significant deviations from the planned assessment times due to the short time frame available to the patients for completion. At each time point, only about 35-45% of those who returned the questionnaire, completed it within the planned time frame.

In order not to compromise the scientific validity of the study, as incorrect timing of QL assessments in chemotherapy oncological trials can jeopardise both the reliability of the QL findings within treatment and the validity of QL outcome comparisons between treatments, the design of the timing of QL assessments in the study have been revised. The main difference is simplifying the schedule of data collection. Patients will complete the QL questionnaires at baseline, end of 1st treatment phase, end of 2nd treatment phase, at 12 and 24 months after randomisation. The second phase of the QL sub-study will aim to recruit further new 1,000 patients.

Patients already recruited in the first phase of QL sub-study between December 2005 and March 2007 (n=778) will continue to receive booklets at the appropriate follow-up time points. Their data, cannot be used for the primary QL analysis, as assessment times of the two phases of the study will be different, but all the data collected will be used for other analyses of equal scientific interest, and for this reason we would want to complete the data collection from patients who have already enrolled on the initial QL schedule. For example as QL assessments coincide with the occurrence of relevant symptoms, the availability of data reflecting functioning, symptoms and global health status of patients at different time point will permit:

- an estimation of the nature and magnitude of the error produced by the ”incorrect” timing the QL assessments in patients receiving accelerated and standard chemotherapy schedule, E-CMF and E-X.
- comparison of changes in QL outcomes overtime in the two phases of the QL study. This will also confirm the validity of the timing used.

The revised second phase of the QL study is described below.

Background

To inform patients of the options available in the adjuvant treatment of early breast cancer, not only is it important to know the survival benefits of systemic therapy, but also the impact such therapy will have on their quality of life (QL). For example, in the Canadian NCIC study of CEF versus CMF, the more active treatment was associated with more toxicity but the additional impact of this upon the patients’ QL disappears within a few months of completing adjuvant treatment [1].

Fatigue has been recognised as a significant and debilitating side-effect of chemotherapy, which in many patients can persist for a considerable time after completion of treatment and can have a major impact on functioning and psychological recovery [2,3]. The possibility that there may be differences in fatigue across treatment modalities has been suggested, comparing chemotherapy and radiotherapy with radiotherapy alone [4]. Women who received chemotherapy and radiotherapy had greater fatigue severity and disruptiveness than women receiving radiotherapy alone. It can be hypothesised that different chemotherapy drugs, different intensity and duration of adjuvant chemotherapy may have different impact on fatigue. For example, dose-intense chemotherapy (CEF14) induced a higher, though transient psychological distress when compared with CEF21 [5]. Therefore, more detailed evaluation of fatigue proposed in TACT2 will help us to examine these effects.

Rationale

To compare QL in each of the 4 treatment groups. With the exception of a trial specific evaluation of the impact of toxicities, similar to that used for the TACT trial, all other instruments to be used are validated questionnaires.

Assessments during treatment will compare the impact on QL of:

- Accelerated treatment versus standard treatment. Accelerated epirubicin is expected to be more effective treatment, but it is not known what is the impact on QL.
- Capecitabine versus CMF after completing 4 courses of epirubicin. The hypothesis is that capecitabine will be equally effective as CMF regimen but less toxic with less impact on QL.

Follow up assessments completed after treatment aim to determine if and when QL returns to baseline levels.

Design

The Quality of Life questionnaires to be used are:

- EORTC QLQ-C30 (version 3) [6]
- EORTC-Breast Cancer Questionnaire (EORTC QLQ-BR23) [7]
- Hospital Anxiety & Depression [8]
- Trial specific evaluation of impact of toxicities on QL
- EuroQoL [9]
- Fatigue questionnaire - Fatigue Symptom Inventory (FSI) and Wu Cancer Fatigue Scale (WCFS) [10-12]

Procedure

Baseline assessments

All patients in the QL study should complete a baseline questionnaire booklet, which incorporates a demographic form, in clinic after giving informed consent, but before randomised treatment allocation is known. The completed questionnaire booklet should be posted to the QL coordinator as soon as the patient is randomised and the patient's trial number is known.

In order to get the precise date of administration of the first cycle of chemotherapy in all patients in the QL study, nurses will send a postcard to the QL centre for each patient in the QL sub-study containing the trial ID number, treatment arm (as a check) and date of administration of their first cycle. No other patient identification data will be contained to permit anonymity.

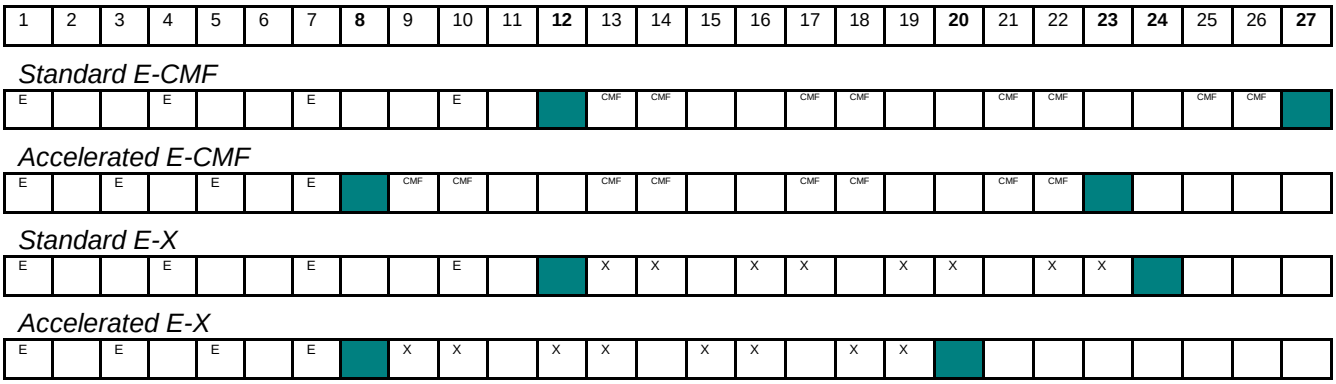
All subsequent questionnaire booklets (i.e. those due for completion during and after chemotherapy treatment) will be sent out by post to patients' home addresses (as supplied on the demographic forms) by the QL coordinator based at CaCTUS in Edinburgh.

Assessments during the treatment phase

Timing

Each patient should complete 2 questionnaire booklets during chemotherapy treatment. These should be at the end of epirubicin treatment, immediately before switching to the second phase and at the end of the second phase (either CMF or capecitabine). The timing of chemotherapy cycles varies depending on treatment allocation, and the weeks during which patients receive active chemotherapy treatment will vary accordingly, as shown below:

Week during which active chemotherapy treatment is given:



Shaded boxes are those weeks in which QL assessments are to be made.
E = epirubicin
CMF = cyclophosphamide, methotrexate and 5-FU
X = Xeloda (capecitabine)

Purpose and precision of timing for each assessment

Assessment time point	What the assessment aims to compare	Precise timing for patients to complete assessments
End of 1st phase Week 8 (if accelerated) Week 12 (if standard)	Impact of schedule intensity after treatment. Also a baseline for comparison with the assessment during second phase of chemotherapy.	The week before day 1 of cycle 5 of chemotherapy (ie last week of cycle 4). Ideally completion should be on last day of this week, but a window of 1 week is acceptable.
End of 2nd phase* Week 20 (if accelerated & capecitabine) Week 23 (if accelerated & CMF) Week 24 (if standard & capecitabine) Week 27 (if standard & CMF)	Impact on QL of capecitabine compared with CMF*. Within-patient comparisons of QL during 1st and 2nd phases of chemotherapy.	The week after chemotherapy was completed (i.e. week 3 of last chemotherapy cycle)

* The difference in time of QL administration in the four arms will be taken into account in the statistical analysis. Detailed methods will be specified in the Statistical Analysis Plan.
For patients who fail to complete eight cycles of chemotherapy, the QL booklets will still be administered at the same expected time-point as they would have been had chemotherapy been delivered as per protocol, in order to avoid any bias due to data collection at different time-points.

After the end of chemotherapy treatment QL will be measured at 12 months after randomisation (see below), which allows for all radiotherapy to have also been given, and this time point will act as a check as to the proportion of patients whose QL has reverted to baseline levels after the various treatments. This will also accommodate delays in chemotherapy administration due to toxicity.

Final QL assessment will be 24 months after randomisation.

Patients who complete QL assessments outside the specified timescale will be included in the QL analysis on an “intention to complete” basis. A second analysis will be performed that excludes QL data that has been completed at least one chemotherapy administration outside the intended timeframe, or in the case of the post-cycle 8 of chemotherapy assessment, after any radiotherapy has been started.

Assessments during the follow up phase

These are at 12 months and 24 months after randomisation. The QL coordinator will contact patients' GPs and / or hospital clinic staff before booklets are sent to patients to confirm that they are alive and well enough to receive them.

Any patient scoring 19 or more at any time point on the combined HADS anxiety/depression scale is at risk of significant psychological morbidity. The patient's oncologist and/or GP will be informed should this occur.

Responsibilities of participating centres

Individual centres may opt to participate in the QL Study. Within those centres, all patients invited to take part in the main trial and able to complete the QL questionnaires (i.e. able to read and understand English) should be invited to take part in the QL study. However, patients may decline entry into the QL Study but still participate in the main study.

Baseline:	Patients must complete the baseline booklet before the treatment allocation is known. The demographic form should be completed by the patient, and the clinic nurse should ensure that treatment details are recorded on the questionnaire booklet, and the trial number is recorded on both the baseline booklet and the demographic form. Both the booklet and demographic form should be sent to the QL coordinator immediately after randomisation.
Treatment phase:	Pre-printed freepost postcards provided by the QL coordinator should be completed and returned to the QL coordinator on day 1 of cycle 1, and on day one of each cycle immediately preceding the next QL assessment. These cards are to confirm the exact date of day 1 of the chemotherapy cycle immediately preceding the next QL assessment. Receipt of a pre-printed card will also be taken as confirmation that a patient is fit and well enough to receive the next QL assessment. Principal investigators are responsible for informing the QL coordinator of any patient unable to complete further questionnaires because they are unfit to receive them or because of treatment related deaths.
Follow up phase:	the QL coordinator will contact participating centres just before follow up assessments are due to confirm that patients are fit and well enough to receive them.

The Principal Investigator at centres opting to participate in the QL study should ensure that staffing allows for the above responsibilities to be met.

Sample size

The detailed sub-study will aim to include 1000 patients and has been powered according to the requirements for the QL component of the analysis. It is believed however that this number is sufficient to provide reliable estimates of toxicity and health services resource use. 1000 patients entered should provide complete–case data on over 800-850 patients i.e. 80%-85% of patients will complete the 12 month assessment (based on the TACT trial compliance figures). It is possible that there will be some carry-over effect between the treatments therefore power has been calculated to look at 4 separate groups of 200-213 patients completing the 12 month assessment. This will provide 92%-94% power to detect a difference of 20% or more (e.g. from 40% to 60% or 45% to 65%) in any proportion at the 1% significance level. Differences of 18% could be detected with 82% power. If there were

no carry over effect and it was possible to look at treatments combined there will be 99% power to detect a difference of 20% or more (e.g. from 40% to 60% or 45% to 65%) in any proportion at the 1% significance level. Differences of 13% could be detected with 82% power. Differences of 5 points or greater in QL scores between the E-CMF and accelerated treatment are considered clinically relevant. A mean difference of 5 points with a standard deviation of approximately 19 (consistent with preliminary data from the TACT QL study) would equate to a standardised difference of 0.27. The 800 - 850 patients in this comparison (400 or 425 in each arm) could detect a difference of 0.27 or more with at least 90% power (alpha = 0.01). If a smaller standard deviation were observed the detectable standardised difference would be larger and hence the power of the study will be greater than 90%.

The intention of the second phase of the QL sub-study is to recruit 1000 patients, which will give 90% power to detect a difference of 12% or more in any proportion at the 1% significance level. The type 1 error chosen, allows, to some degree, for multiple testing involved in analysing individual sub-scales of the QL questionnaires. If it appears that it will be possible to recruit more than 1000 patients in the second phase of the QL sub-study, MREC will be contacted to seek permission to continue recruitment beyond that figure if it appears feasible.

The primary analysis in the QL Study will compare the overall QL and HADS scores. The time dependency of the data will be acknowledged by using a generalised linear modelling approach. Missing data will be handled according to recommended standard EORTC procedures.

References

1. Levine MN, Bramwell VH, Pritchard KI, Norris BD, Shepherd LE, Abu-Zahra H, Findlay B, Warr D, Bowman D, Myles J, Arnold A, Vandenberg T, MacKenzie R, Robert J, Ottaway J, Burnell M, Williams CK, Tu D. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. National Cancer Institute of Canada Clinical Trials Group.J Clin Oncol. 1998; 16(8):2651-8.
2. Broeckel JA, Jacobsen PB, Horton J, Balducci L, Lyman GH. Characteristics and correlates of fatigue after adjuvant chemotherapy for breast cancer. J Clin Oncol. 1998; 16(5):1689-96.
3. Fan HG, Houede-Tchen N, Yi QL, Chemerynsky I, Downie FP, Sabate K, Tannock IF. Fatigue, menopausal symptoms, and cognitive function in women after adjuvant chemotherapy for breast cancer: 1- and 2-year follow-up of a prospective controlled study. J Clin Oncol. 2005; 23(31):8025-32.
4. Donovan KA, Jacobsen PB, Andrykowski MA, Winters EM, Balducci L, Malik U, Kenady D, McGrath P. Course of fatigue in women receiving chemotherapy and/or radiotherapy for early stage breast cancer. J Pain Symptom Manage. 2004; 28(4):373-80.
5. Del Mastro L, Costantini M, Morasso G, Bonci F, Bergaglio M, Banducci S, Viterbori P, Conte P, Rosso R, Venturini M. Impact of two different dose-intensity chemotherapy regimens on psychological distress in early breast cancer patients. Eur J Cancer. 2002; 38(3):359-66.
6. Aaronson NK et al. The European Organisation for the Research and Treatment of Cancer QLQ-C30: A quality of life instrument for use with international clinical trials in oncology. J Nat Cancer Inst. 1993; 85:365-376

7. Sprangers MAG Groenvold M Arraras JI Franklin J Velde A Muller M Franzini L Williams A de Haes HCJM Hopwood P Cull A Aaronson NK. The European Organisation for Research and Treatment of Cancer Breast Cancer-Specific Quality-of–Life Questionnaire Module: First results from a three-country field study. J Clin Oncol. 2001; 5:917-929
8. Zigmond AS & Snaith RP . The Hospital Anxiety and Depression Scale. Acta Psychiatr Scand 1983; 67:361-370.
9. EuroQoL Group. EuroQoL - a new facility for the measurement of health-related quality of life. Health Policy 1990; 16: 199-208
10. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. Qual Life Res. 2000; 9(7):847-54.
11. Wu HS, McSweeney M. Assessing fatigue in persons with cancer: an instrument development and testing study.Cancer. 2004; 101(7):1685-95.
12. Wu HS, Wyrwich KW, McSweeney M. Assessing fatigue in persons with cancer: further validation of the Wu Cancer Fatigue Scale. J Pain Symptom Manage. 2006; 32(3):255-65.

APPENDIX 2 Sub-study 2: Biology

Paraffin blocks

Standard pathological information will be collected at randomisation on all patients entered into the trial. This information will also include the histology number, location of paraffin tumour blocks and reporting consultant pathologist (if known). This will enable the prospective construction of tissue microarrays (TMAs) for storage and analysis at a later date. This method of collection has already proved successful in the Taxotere as Adjuvant Chemotherapy (TACT) Trial. Tissue sections will be tested using immunohistochemical techniques for the presence of standard biological predictive markers of treatment benefit such as EGFR, HER-2 and p53.

There are a number of other hypotheses which can be tested in the bank of TMAs obtained from patients in this trial, relating to markers predicting for potential sensitivity to the agents used in this trial, such as Thymidine Phosphorylase and Topoisomerase IIα. However other studies are currently in progress that will refine such hypotheses, and therefore it is felt that it would not be appropriate to define them in precise terms at this stage.

Blood samples

A single blood sample will be collected and stored at -80°C at a central laboratory for future screening of DNA polymorphisms in all (consenting) patients. DNA will be prepared from the samples and can be used to look for polymorphisms in the genes encoding the enzymes that metabolise and/or activate the chemotherapeutic agents administered. For patients in the pharmacokinetic sub-study, validation will be carried out by comparing the observed Pharmacokinetics with the DNA polymorphisms. For all patients, the polymorphisms will be compared with the observed toxicity, hypothesising that variation in DNA sequence that might be predictive of those that suffer more extreme toxicity, perhaps even identifying those for whom certain drugs should be avoided. Once outcome data are available, the data will then be analysed in conjunction with the observed benefits from adjuvant capecitabine and/or accelerated treatment, controlling for standard recognised risk factors. This has the potential to define a subset of patients with the most or the least to gain from the trial treatments.

All patients will be invited to take part in both aspects of the biological studies, but may still enter the main trial if they do not want to participate in the biological sub studies.

APPENDIX 3 Sub-study 3: Cost Consequences of Trial Participation

The introduction of capecitabine and / or GCSF in the TACT2 trial of adjuvant treatment for breast carcinoma involves additional cost of some drugs, but trial drug costs have the potential to be offset by the reduced cost of treating treatment related toxicity and relapsed disease.

It is anticipated that oral administration of capecitabine therapy will provide advantages over IV administration of CMF with respect to medical resource utilization, due to avoidance of clinic cost for staff time, IV supplies, administration time, etc. In particular, oral therapy may provide a significant advantage with respect to resource utilization for patients whilst on oral cytotoxic therapy once they have completed their IV chemotherapy regimen, since the oral capecitabine therapy will likely require less hospital visits and/or visits of shorter duration than the IV therapy.

Estimated NHS costs on which to base hypotheses

Estimate of added NHS treatment costs for patients in this study (estimates correct as of December 2003).

ARM	**No. of out-patient chemo visits**	**Drug costs**	**Estimated rate of Neutropenic sepsis**
E-CMF (as per NEAT)	12	Standard	13%
E(a)-CMF	12	+£840	3% + 6% = 9%
E-X	8 + 1 toxicity check	- £350	6% + 2% = 8%
E(a)-X	8 + 1 toxicity check	+£ 840-£350	3% + 2% = 5%
Average	**10.5 visits**	**£245 per patient**	**8.75%**

Data:

Cost of one dose of Neulasta (Pegylated GCSF) £840 (next 3 free)

Estimated cost of Classical CMF (@Beatson Oncology Centre) £350
(Not including giving sets etc.)

Estimated cost of admission for neutropenic sepsis £1440
(Heather Dalrymple, WGH Pharmacy, Edinburgh)

Drug costs of neutropenic sepsis per patient admitted £425

Neutropenic sepsis rate for 8 cycles of E-CMF was 13% in Neat trial, and 10% for 6 cycles of CMF. These data suggest that the rate is around 1.5% per cycle. Accelerated chemotherapy appears to reduce this by 50% in CALGB 9741, which would give a rate of 0.75% per cycle of accelerated epirubicin. Capecitabine is associated with an extremely low rate even in advanced disease, but allowing for possible admissions for diarrhoea, we have estimated the rate at 0.5% per cycle.

Thus on average enrolling patients in this trial reduces the number of visits by 1.5, requires an extra £245 of direct drug costs, and reduces the incidence of neutropenic sepsis by perhaps 4.25%, providing a direct saving of around £18 per patient, and additional release of resources of £50 per patients in reduced bed costs, plus the reduced day case requirement. This does not include the cost of GCSF in the non-accelerated arms and pegylated GCSF will also be available at a price of £840 for the first dose with the next 3 doses free. The frequency of such use is not known, but would be a cost benefit to trusts that would need to be offset against the slight increase in total drug costs for patients in this study.

Therefore we estimate that the extra costs to institutions to be around £230 per patient in direct drug costs. For a trust recruiting perhaps 40 patients per year this equates to approximately £10, 000 per annum. The value of resource released will approximate to at least £3,000 for the same number of patients (excluding transport costs).

Health Economic Evaluation

A health economic evaluation will be carried out after the main trial has completed recruitment, and will be the subject of a separate funding application. Data collection is prospective and incorporated in the trial design but the extent of the economic analysis will be dependent on clinical outcome of the trial. It will take the form of a cost-consequences analysis and of a cost-effectiveness analysis. In the former, the differential resource use and cost of the alternative management strategies will be presented alongside the range of clinical and health-related quality of life (HRQL) effects. In the latter, the differential cost of the alternative treatments will be related to their differential benefits in terms of quality-adjusted life years (QALYs), and standard cost-effectiveness acceptability curves will be used to show the probability of one option being more cost-effective than the other.

Estimating resource use

Resource use measurement during the trial will be collected in a similar fashion to the FOCUS trial [1] and is divided into four components: hospital; NHS non-hospital; patient travel costs and patient productivity costs. These are dealt with in turn below.

Hospital resource use

The dominant costs in chemotherapy treatment are likely to be inpatient stay and high cost drugs [2]. There are potentially different rates of inpatient stay related to toxicity of treatment in this trial, and potential differences in admissions for management of recurrent disease depending on the clinical outcome of the trial. These costs are being collected on all patients in trial through the chemotherapy details, the adverse event reporting of admissions and the questions as to admissions on the annual follow up reports. Data collected will include stays in hospital related to non-study hospitals.

Because capecitabine is taken at home and requires fewer hospital attendances then data on patient travel distances, economic circumstances and whether patients are accompanied on hospital visits will be collected on those patients in the quality of life study enabling an economic evaluation with a societal perspective.

NHS non-hospital resource use

Patients' use of community-based NHS services will be collected from patients participating in the Quality of Life study in the form of a short questionnaire incorporated in the Quality of Life questionnaire booklets administered during treatment and follow up. The resources will include visits to and from a GP or district nurse.

Patient travel costs

There will be differences in hospital visits between trial arms. Patients' travel costs will be estimated using a cost per hospital visit and multiplying that cost by the number of occasions each patient visits hospital. In order to cost a given visit to hospital for each patient, a short questionnaire will be administered at baseline. This will collect information on the typical mode(s) of transport, distance and time of journeys to hospital, and whether the patient had a companion. Based on these data, patients' travel costs will be based on published unit costs for travel.

The questionnaire will also collect information to cost the time patients and any companions allocate to the visit.

Patient productivity costs

The number of days during which patients are unable to undertake their usual activities because of illness will be established at the various points of follow-up. In addition, it will be necessary to ask patients at baseline what their usual activity is.

Measuring effects

The clinical trial is estimating a range of clinical and HRQL effects in trial patients. The purpose of the economic evaluation will be to set these in context of the resource costs incurred in achieving them. Cumulative costs will be shown in the form of a timeline from randomization. A cost-effectiveness analysis will relate differential cost to an aggregated measure of effect in the form of a quality-adjusted life-year (QALY).

References:

1. FOCUS 1 and FOCUS 2 Clinical Protocol MRC Clinical Trials Unit – professor Mark Sculpher, Advisor Economic Evaluation.
2. Bloomfield DJ. Krahn MD. Neogi T. Panzarella T. Smith TJ. Warde P. Willan AR. Ernst S. Moore MJ. Neville A. Tannock IF. Economic evaluation of chemotherapy with mitoxantrone plus prednisone for symptomatic hormone-resistant prostate cancer: based on a Canadian randomized trial with palliative end points. [Clinical Trial. Phase III. Journal Article. Multicenter Study. Randomized Controlled Trial] Journal of Clinical Oncology. 16(6):2272-9, 1998 Jun.

APPENDIX 4 Sub-study 4: Evaluation of Cardiac Function

Anthracyclines are well known to be cardiotoxic, although milligram for milligram epirubicin is less so than adriamycin [1]. The risk factors for cardiotoxicity are increasing age, high BMI, pre-existing cardiac disease and cumulative dose of anthracycline. Dose intensity within the range of 25 mg/week and 35 mg/week has not been shown to be an issue in retrospective studies [2].

Capecitibine also has cardiac effects, but these relate to induction of coronary artery spasm rather than direct myocycte toxicity as with the anthracyclines. Nevertheless if pre-existing coronary artery disease is present such spasm may be sufficient to induce myocardial injury. The cardiac effect of capecitibine after anthracyclines is not known, although anthracyclines may cause increases in thymidilate synthetase levels increasing the potency of capecitibine.

The TACT2 trial gives an opportunity to prospectively study the cardiac effects of epirubicin dose intensity and also refine the relative contributions of other potential variables which may affect cardiotoxicity.

Methods

Centres which have routinely performed pre-chemotherapy LVEF estimations will repeat these at 2.5 – 3 years post-randomisation. Other data that will be collected is as follows:

- Age, smoking history, BMI will be available from the existing CRFs
- Blood pressure pre- first cycle of chemotherapy will be obtained from the nursing records
- Cardiac history and medications will be obtained from the case notes, and rechecked at the time of ordering the repeat LVEF, BMI will be re-calculated at that time

Patients who subsequently received adjuvant Herceptin will be included but analysed as a separate group.

The risk of developing any degree of cardiac problem as defined by the NY scale will be analysed by treatment arm. Single and Mulivariate anaylsis will be performed to also include known non-chemotherapy risk factors: age, pre- and post- chemotherapy BMI, smoking history, hypertension, use of adjuvant Herceptin.

Any patient known to have died with or due to cardiac illness will also be included in the analysis.

References

1. Von Hoff DD. Layard MW. Basa P. Davis HL Jr. Rozencweig M. Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Annals of Internal Medicine. 91(5):710-7, 1979 Nov.
2. Fumoleau, P. Roche, H. Kerbrat, P. Bonneterre, J. Romestaing, P. Fargeot, P. Namer, M. Monnier, A. Montcuquet, P. Goudier, M-J. Luporsi, E. French Adjuvant Study Group. Long-term cardiac toxicity after adjuvant epirubicin-based chemotherapy in early breast

cancer: French Adjuvant Study Group results. Annals of Oncology. 17(1):85-92, 2006 Jan.

APPENDIX 5 Radiotherapeutic Procedures

1 General/Timing

Irradiation should be postponed until systemic treatment is completed. Ideally, it should commence 4 weeks after the last cycle of chemotherapy commences, or after any planned post-chemotherapy surgery. However, it should start no later than 6 weeks after the last cycle of chemotherapy.

2 Radiotherapy indications

2.1 Chest wall radiotherapy

Chest wall radiotherapy following mastectomy should be considered for patients who fit any one of the following criteria [39]:

- T3 tumours
- Four or more axillary nodes involved
- Involved margins
- 1 – 3 nodes involved with the addition of any one of:
    - Lymph-vascular invasion
    - High grade tumours
    - Patients otherwise eligible for SUPREMO would be allowed to receive XRT or not as determined by that randomisation

2.2 Radiotherapy to the breast itself

This is an integral part of any breast-conserving procedure and should be performed in all cases.

2.3 Nodal radiotherapy

Radiotherapy must include the axilla if an axillary sample has been positive and a full (usually level III) surgical clearance has not been performed. In these cases, it is strongly recommended that a treatment technique is used which minimises any overlap, and that the match interface should not involve the axilla, a potential disease site.

Radiotherapy to the axilla after a full level III axillary dissection must be avoided unless there is evidence of macroscopic residual disease in the axilla.

Irradiation of internal mammary nodes should be avoided so as to minimise the radiation dose to myocardium and lung.

Extracapsular spread in patients with involved axillary nodes does not constitute an absolute indication for axillary radiotherapy after surgical clearance of the axilla, given the higher risks of lymphoedema in these circumstances, and the lack of any evidence of survival benefit. Any treatment must only be considered after careful discussion with the patient on an individual patient basis.

Another controversial area is the case for a supraclavicular field in patients with more than three axillary nodes involved, especially, perhaps, those with apical node involvement. However, we feel it would be inappropriate to proscribe these practices and it is recognised such decisions have to be made on a case-by-case basis. If fraction sizes greater than 2 Gy are used, then total dose applied to the supraclavicular field must be reduced appropriately.

A suggested treatment planning protocol for this contingency may be found below. We recognise this approach is increasingly employed for an involved sentinel node, or involved node(s) at sampling, as an alternative to formal axillary clearance.

3 Technique

3.1 Position of the patient

The patients will be treated in the supine position. This position should be reproduced during simulation, acquirement of planning CT (if used) or contour and treatment. It is advised to assess the reproducibility by orthogonal laser beams.

3.2 Chest wall / Breast field.

Tangential fields will be used. Irradiation of large volumes of lung by the tangential fields should be avoided by keeping the central lung distance to less than 3 cm.

For patients with left-sided tumours, the irradiation of large volumes of heart must be avoided by keeping the distance from the posterior edge of the field to the anterior border of the heart to <1.5 cm. If these parameters cannot be met, then we recommend that either full CT planning or the use of a lead cardiac shield on the medial field should be used.

A simulator film or digital image must be taken on the medial field to verify the above parameters have been met. A minimum of one transverse outline, taken on the central axis of the length of the tangential fields should be taken.

3.3 Axilla and supra-clavicular field.

Where the clinician feels these are a necessity, an anterior supraclavicular field with an opposed posterior axillary field will be used. The upper border will cover the supraclavicular fossa and is about 3 cm above the head of the clavicle. It is suggested that a gantry angle (usually of about 15%) is used to angle the field away from the spine. The medial border is the ipsilateral edge of the vertebral bodies. The lateral border should be placed at the insertion of Teres major onto the humerus. The lower field border should be matched onto the upper border of the tangential fields. If no chest-wall fields are to be used, then the lower border of the supra-clavicular field should be at the level of the lower end of the head of the clavicle. The posterior axillary field should cover the apex of the axilla superiorly, the lower edge of anterior supraclavicular field inferiorly, and about to the lateral ends of the ribs medially. The use of a surgical clip is ideal to define the lower border of radiotherapy and upper border surgery, in the event of a level one clearance/sampling. Any shielding blocks will be indicated on a simulation film.

3.4 Supra-clavicular field.

Where the clinician feels this is a necessity, a single anterior field will be used. The infero-lateral corner should lie at the marker placed at the supra-medial limit of the axillary dissection. The upper border will cover the supraclavicular fossa and is about 3 cm above the head of the clavicle. It is suggested that a gantry angle (usually of about 15%) is used to angle the field away from the spine. The medial border is the ipsilateral edge of the vertebral bodies, the lateral border is guided by surgical clips if available, otherwise at the lateral extent of the second rib. The lower field border should be matched onto the upper border of the tangential fields. If no chest-wall fields are to be used then the lower border of the supra-clavicular field should be at the level of the lower end of the head of the clavical. Any shielding blocks will be indicated on a simulation film.

4 Dose and Fractionation

The dose distribution should be shown at least in the plane through the beam axes. The target area (PTV) in this plane should be outlined.

The tumour dose is specified at the reference point or iso-centre for the tangential fields, to the mid-plane for axillary fields and as an incident dose for the supraclavicular field.
A number of different dose/ fractionation schedules are in routine use. The following schedules are acceptable, to both the breast and nodal fields:

50 Gy / 25 daily fractions over 5 weeks
46 Gy / 23 daily fractions over 4½ weeks
45 Gy / 20 daily fractions over 4 weeks
40 Gy / 15 daily fractions over 3 weeks

or as specified by the protocol of an NCRN-approved radiotherapy protocol.

For patients having had conservative surgery, a boost to the tumour bed may be given in accordance with local protocol.

5 Treatment verification

We recognise that NHS funding constraints mean that verification films are not part of standard practice, in contrast to much of Western Europe and North America. However, where local resources do allow, it is recommended that a weekly portal imaging film (or other recording when using on-line portal imaging systems) be obtained during the course of treatment. Portal films should be compared to the simulator film. Field adjustments should be made in case of clinically important difference. This is not a requirement of the study. It should not discourage clinicians from participating.

6 Alternative methods

Some centres have developed their own specific irradiation techniques for breast, chest wall, and supraclavicular treatments. Irradiation techniques and dosages differing from those described in the protocol, e.g. electron fields for chest wall irradiation, can be allowed, provided a detailed description is given.

Alternative dose schedules are allowed if these are routinely employed by any centre, but the doses must remain constant for all arms of the trial and must be described in advance. The description of any alternative techniques and/or dose/ fractionation schedules will be reviewed by the Steering Committee prior to inclusion as a trial participant.

APPENDIX 6 ECOG Performance Status

Status	Description
0:	Asymptomatic, fully active and able to carry out all pre-disease performance without restriction
1:	Symptomatic, fully ambulatory but restricted in physically strenuous activity and able to carry out performance of a light or sedentary nature e.g. light housework, office work
2:	Symptomatic, ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours: in bed less than 50% of day
3:	Symptomatic, capable of only limited self-care, confined to bed or chair more than 50% of waking hours, but not bed-ridden
4:	Completely disabled. Cannot undertake any self-care. Totally bed-ridden

APPENDIX 7 New York Heart Association Functional Classification

NYHA CLASS:

Class I: Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.

Class II: Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.

Class III: Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.

Class IV: Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 8 Common Terminology Criteria for Adverse Events

In the present study, toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, at the following address:
http://ctep.cancer.gov/reporting/ctc.html

APPENDIX 9 Sample Patient Information Sheet, consent forms & GP letter

These are provided as separate documents.

APPENDIX 10 Compatibility with Other Studies

Given that this trial involves a 2x2 randomisation, there is a concern that patients might find it stressful to have to think about this study and another breast cancer systemic therapy trial at the same time. Therefore, in order to avoid the problem of "over-burdening" patients with trial choices, it is not permitted to enter patients into another systemic therapy trial within two months either side of enrolment in the TACT2 trial, nor to enter into the Quality of Life sub-study of the TACT2 trial if they have already enrolled into an ongoing QL sub-study of another trial. Similarly, if they enrol into the TACT2 Quality of Life sub-study, they should not be enrolled into another trial's QL sub-study.

The following studies are compatible with TACT2:

OPTION

This trial is only open to patients who are pre-menopausal and with ER/PgR negative tumours. It asks the question as to whether the use of a LHRH agonist with the chemotherapy would reduce the risk of premature ovarian failure and its consequent symptoms and QL effects.

REACT

The primary aim of the proposed REACT trial is to assess the disease-free survival benefit of 2 years of adjuvant therapy with celecoxib versus placebo. Possible enrolment and treatment with celecoxib/placebo will commence only on completion of adjuvant chemotherapy for primary breast cancer. The trial will be open to ER negative patients and to postmenopausal ER positive patients. ER positive patients will receive exemestane for 5 years, starting concurrently with celecoxib/placebo, exemestane and/or celecoxib in post-menopausal patients with ER positive breast cancer. The use of aromatase inhibitors in the adjuvant setting is anticipated to increase in the next few years as a result of the data from the ATAC, MA17 and IES exemestane studies, such that entering patients in a trial randomising between tamoxifen and exemestane is not thought to be detrimental to the primary questions of TACT2. Many patients could potentially be enrolled into both the REACT and TACT 2 trials, hence this trial could potentially enrol a lot of patients in TACT2, so that the TMG and IDMC will have to monitor the proportion entering both the studies and whether any selection bias is being introduced to ensure that there is no danger that one study could unduly influence the other. However, since the QL instruments used are different between the two studies, patients in the QL sub-study of TACT2 will not be eligible for REACT.

SOFT

This trial asks the question as to what is the optimum adjuvant endocrine therapy after chemotherapy in pre-menopausal patients with early breast cancer who are still menstruating post-chemotherapy. It is therefore mutually exclusive with the above proposed REACT trial. Potential women already in the TACT2 trial would be enrolled only upon completion of chemotherapy, and are randomised between 5 years' tamoxifen, 5 years ovarian ablation plus tamoxifen, and 5 years' ovarian ablation plus exemestane. Since the

majority of patients anticipated to be enrolled in TACT2 are likely to be older, the proportion of women who would meet this fundamental criteria for SOFT will be a very small group within the whole of the TACT2 population.

SUPREMO

This is an MRC trial of chest wall radiotherapy in patients with 1 – 3 nodes positive. Radiotherapy for these patients is not mandated within TACT2, and so SUPREMO is therefore compatible with TACT2.

IMPORT High

IMPORT high is a Phase III, randomised, clinical trial to test dose escalated intensity modulated radiotherapy (IMRT) after breast conservation surgery and appropriate systemic therapy in woman with higher than average risk of local tumour recurrence risk. Patients are randomised to either the control arm (40Gy to whole breast, 15 treatments over 3 weeks), Test arm 1 (36Gy to whole breast, 40Gy to partial breast, 15 treatments over 3 weeks) or Test arm 2 (40Gy to partial breast, 15 treatment over 3 weeks). The primary endpoint of IMPORT High is different to that of TACT2, being palpable induration in the irradiated breast since this is a common late effect of curative radiotherapy for early breast cancer. Those patients considered at high risk of recurrence may be eligible for entry into IMPORT High after completing chemotherapy. The invitation to take part in would occur during TACT2 follow up, patients taking part in the QL sub-study of TACT2 should not be entered into the IMPORT High QL sub-study.

ALTTO

ALLTO is a Phase III randomised, study of adjuvant lapatanib, trastuzumab, their sequence and their combination in patients with HER2 positive primary beast cancer. Patients are randomised to either (1) trastuzumab for one year, (2) lapatanib for one year, (3) trastuzumab (12 weeks) followed by a 6-week treatment free interval followed by lapatanib or (4) trastuzumab in combination with lapatanib for one year. The primary endpoint of the study is disease-free survival. HER2 positive patients who are planned for treatment with herceptin may wish to take part in ALLTO, the invitation to do so would occur during TACT2 follow up. Although the primary endpoints of both studies are the same, only a small minority of patients in either trial will be enrolled in the two studies, and both trials are randomized therefore the statistical validity of the data is maintained.

POETIC

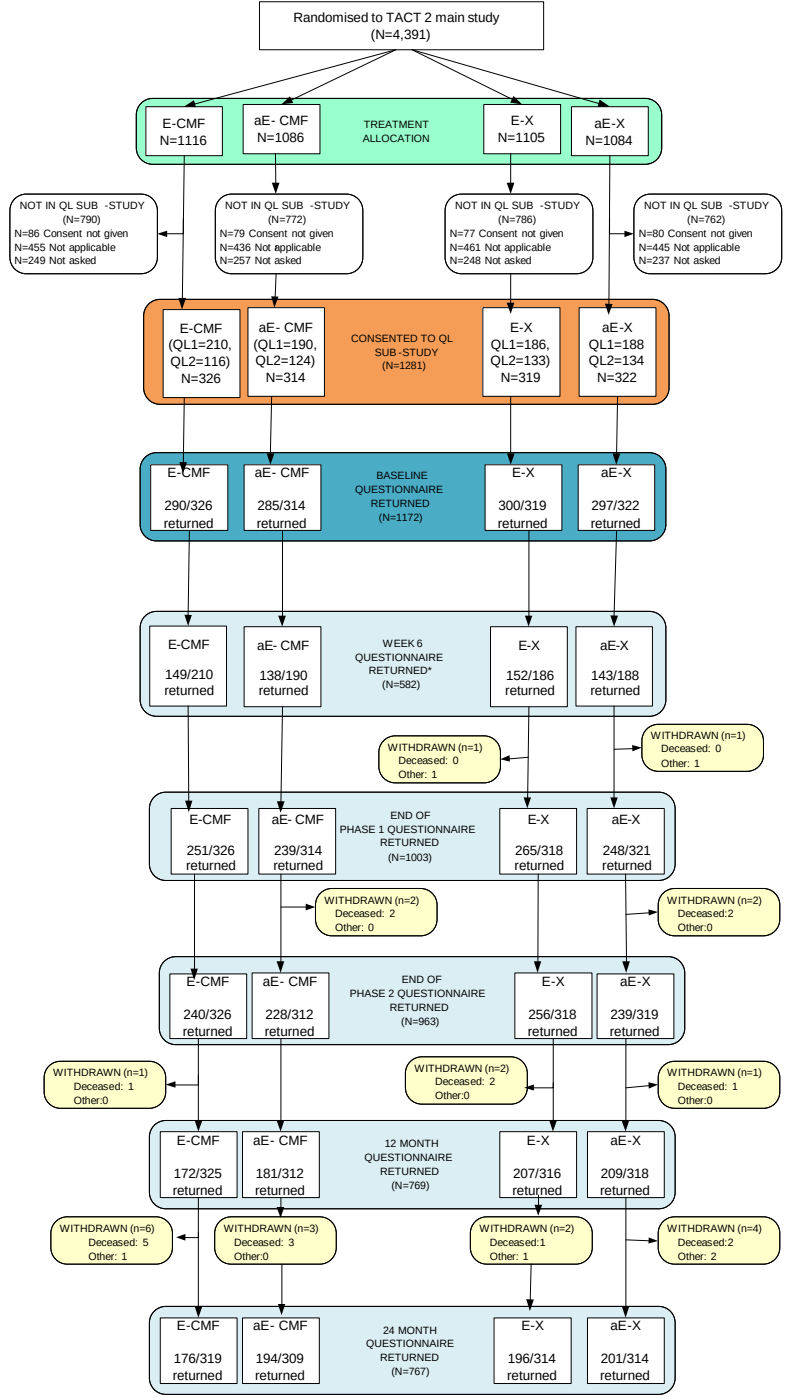
POETIC is a phase III, randomised, clinical trial of peri-operative endocrine therapy in post-menopausal women with ER &/or PgR positive breast cancer. The primary endpoint is to determine whether four weeks perioperative treatment with an aromatase inhibitor will improve the relapse free survival interval compared with standard adjuvant treatment. Patients will be randomised in a 2:1 ratio to receive 2 weeks pre-operative and 2 weeks post-operative treatment with an aromatase inhibitor (either anastrozole or letrozole) versus no perioperative treatment. Patients will be followed up as per local practice for early breast cancer. Patients that participate in POETIC may subsequently wish to participate in TACT2,

MAPLE

MAPLE is a double-blind, short term, pre-surgical study of lapatinib in patients with primary breast cancer. Patients are randomised to receive either lapatinib treatment or placebo for 2 weeks prior to surgery and are then followed up for 30 days post-operatively. The primary endpoint is to identify molecular predictors of the anti-proliferative effects of lapatinib.

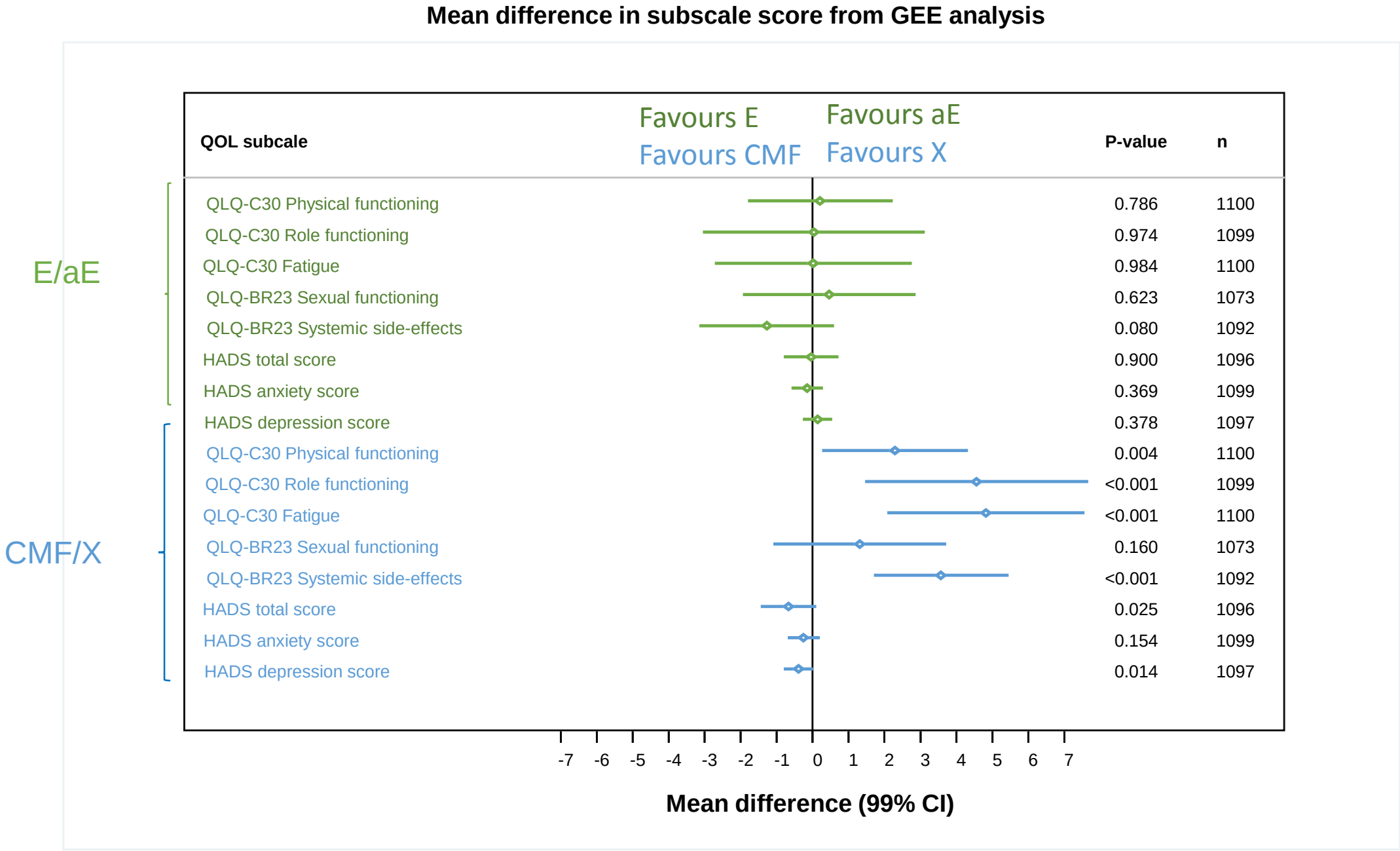
Lapatinib Presurgical (Charing Cross)

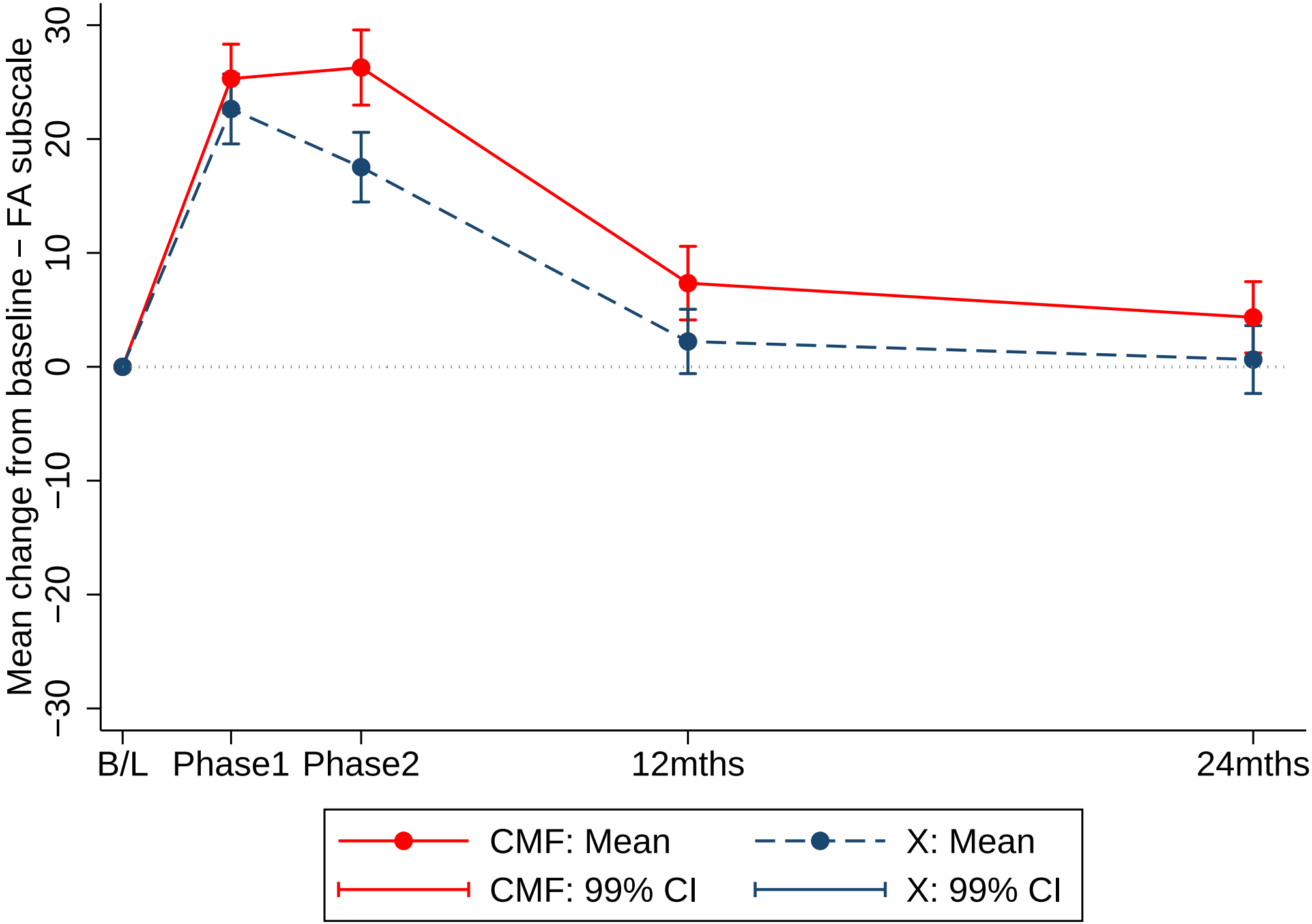
This is a Phase II, pre-surgical, study of lapatinib in patients with primary breast cancer. Patients entered into this trial will be treated for 4-6 weeks prior to surgey with lapatinib then followed up for 30 days post-surgery. The primary endpoint of this study is clinical response as assessed by RECIST after 2 weeks treatment and then prior to surgery.

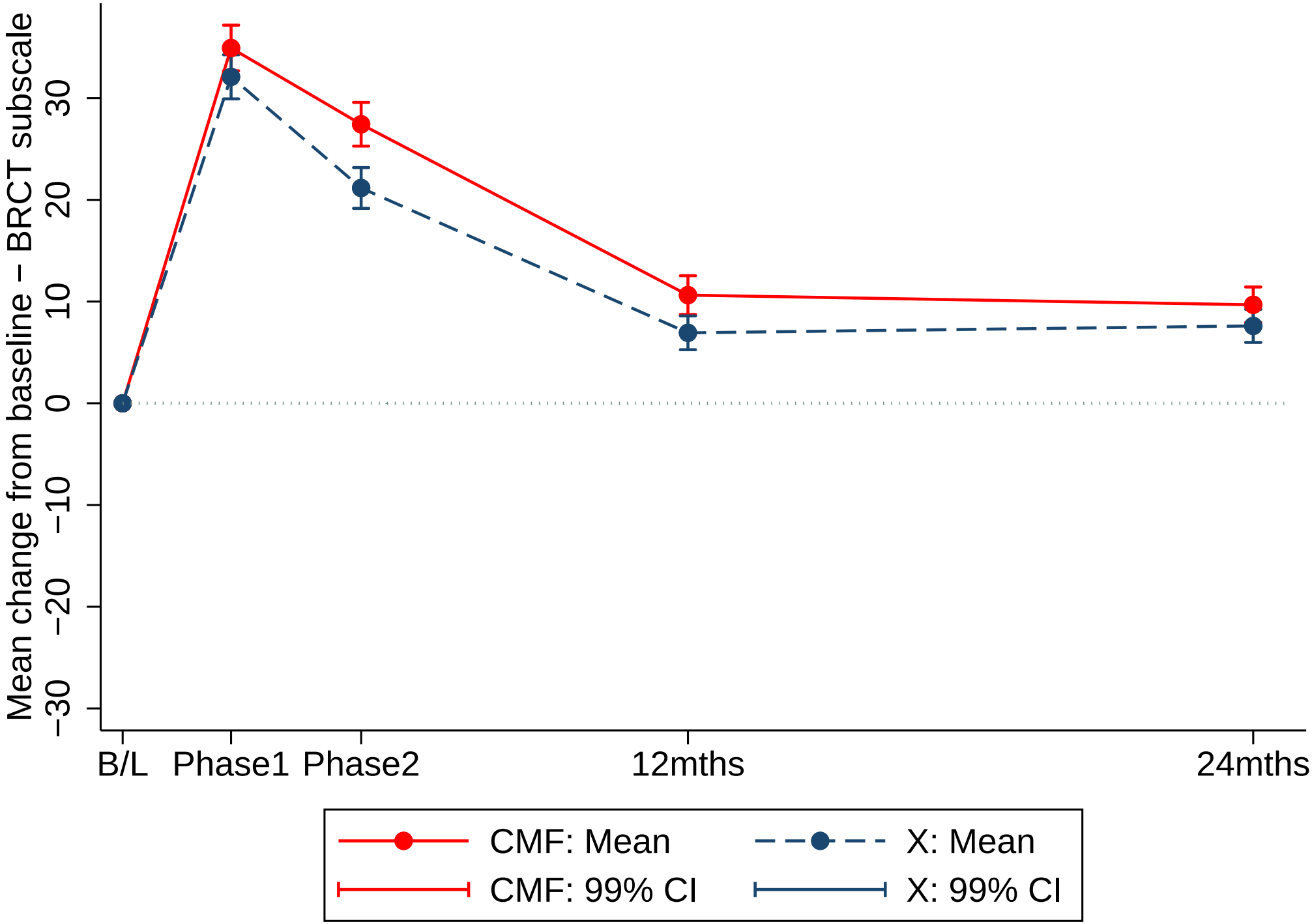


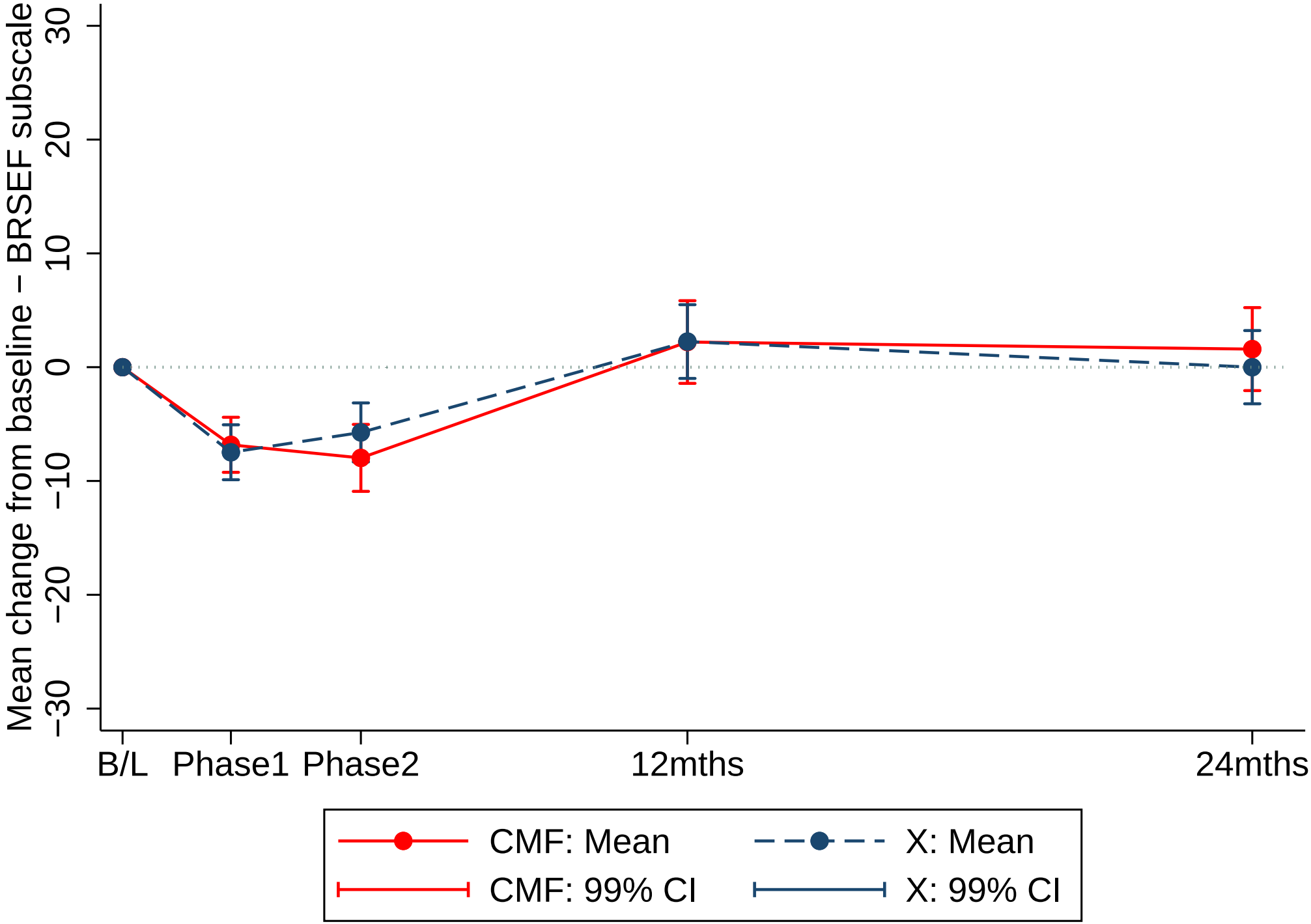
*Week 6 Questionnaires were only sent to patients in the first part of the QL study (QL1)

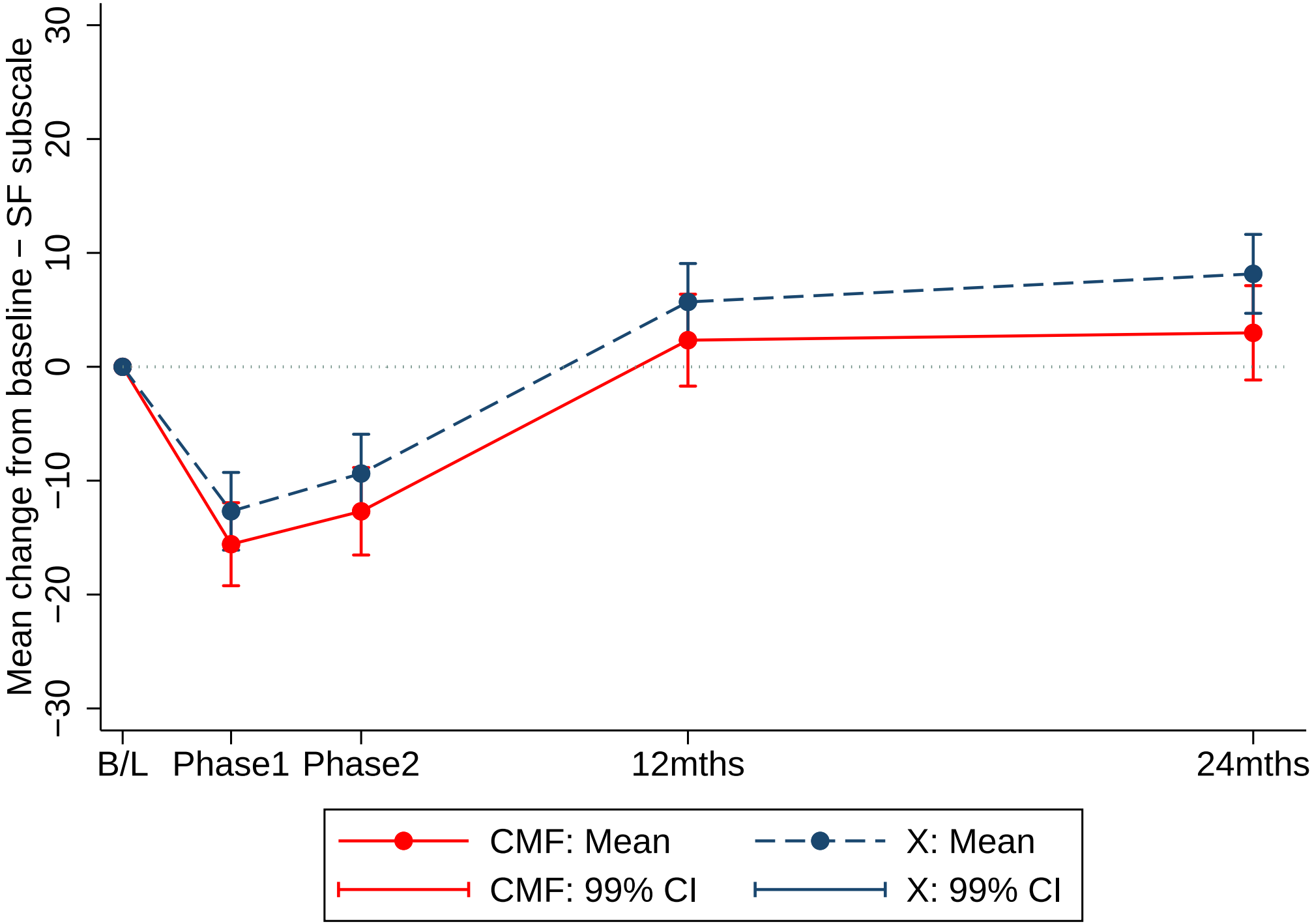
Figure

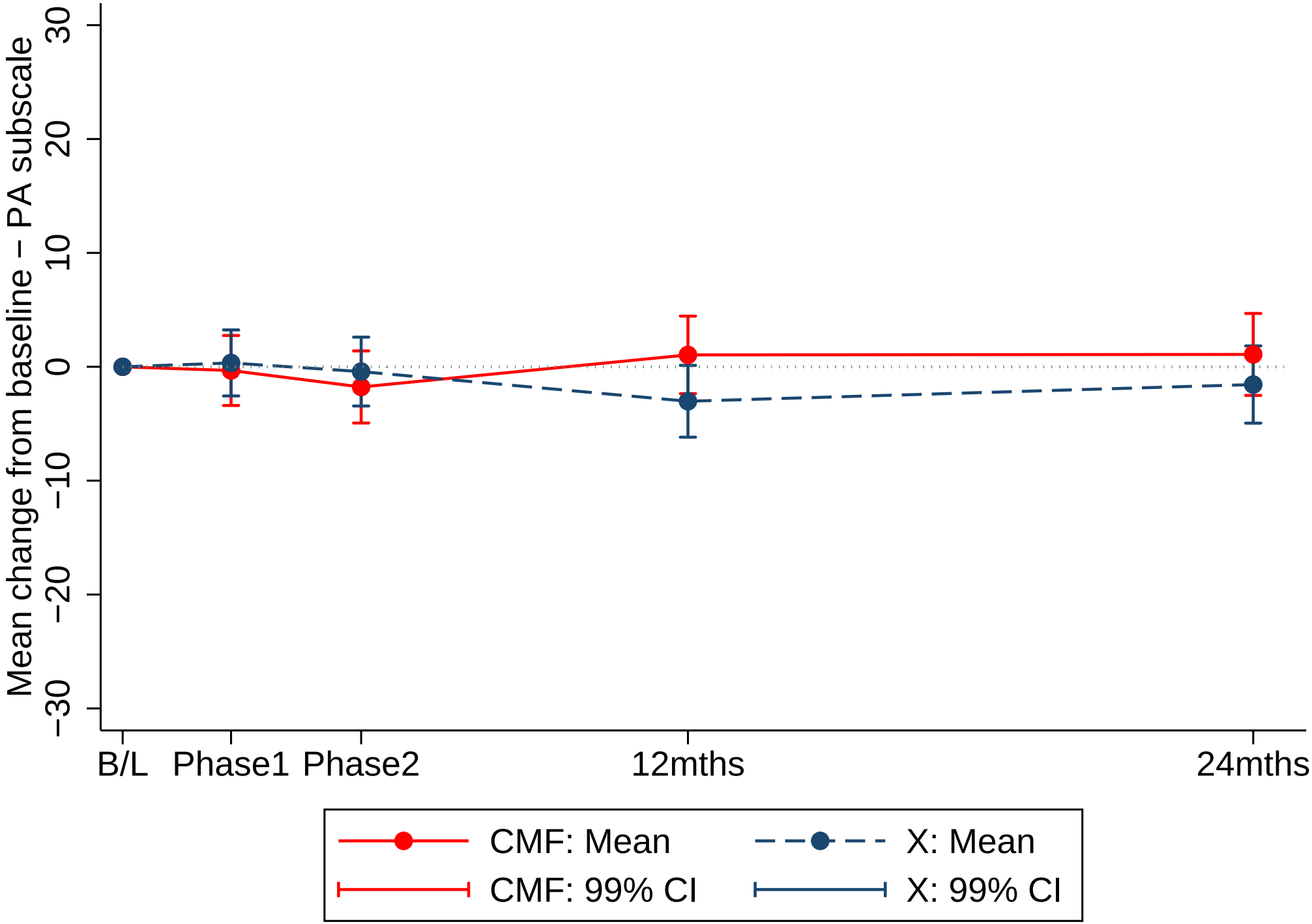

Mean difference in subscale score from GEE analysis
QOL subcale
Favours E
Favours CMF
Favours aE
Favours X
P-value
n
E/aE
CMF/X
QLQ-C30 Physical functioning 0.786 1100
QLQ-C30 Role functioning 0.974 1099
QLQ-C30 Fatigue 0.984 1100
QLQ-BR23 Sexual functioning 0.623 1073
QLQ-BR23 Systemic side-effects 0.080 1092
HADS total score 0.900 1096
HADS anxiety score 0.369 1099
HADS depression score 0.378 1097
QLQ-C30 Physical functioning 0.004 1100
QLQ-C30 Role functioning <0.001 1099
QLQ-C30 Fatigue <0.001 1100
QLQ-BR23 Sexual functioning 0.160 1073
QLQ-BR23 Systemic side-effects <0.001 1092
HADS total score 0.025 1096
HADS anxiety score 0.154 1099
HADS depression score 0.014 1097
-7 -6 -5 -4 -3 -2 -1 0 1 2 3 4 5 6 7
Mean difference (99% CI)

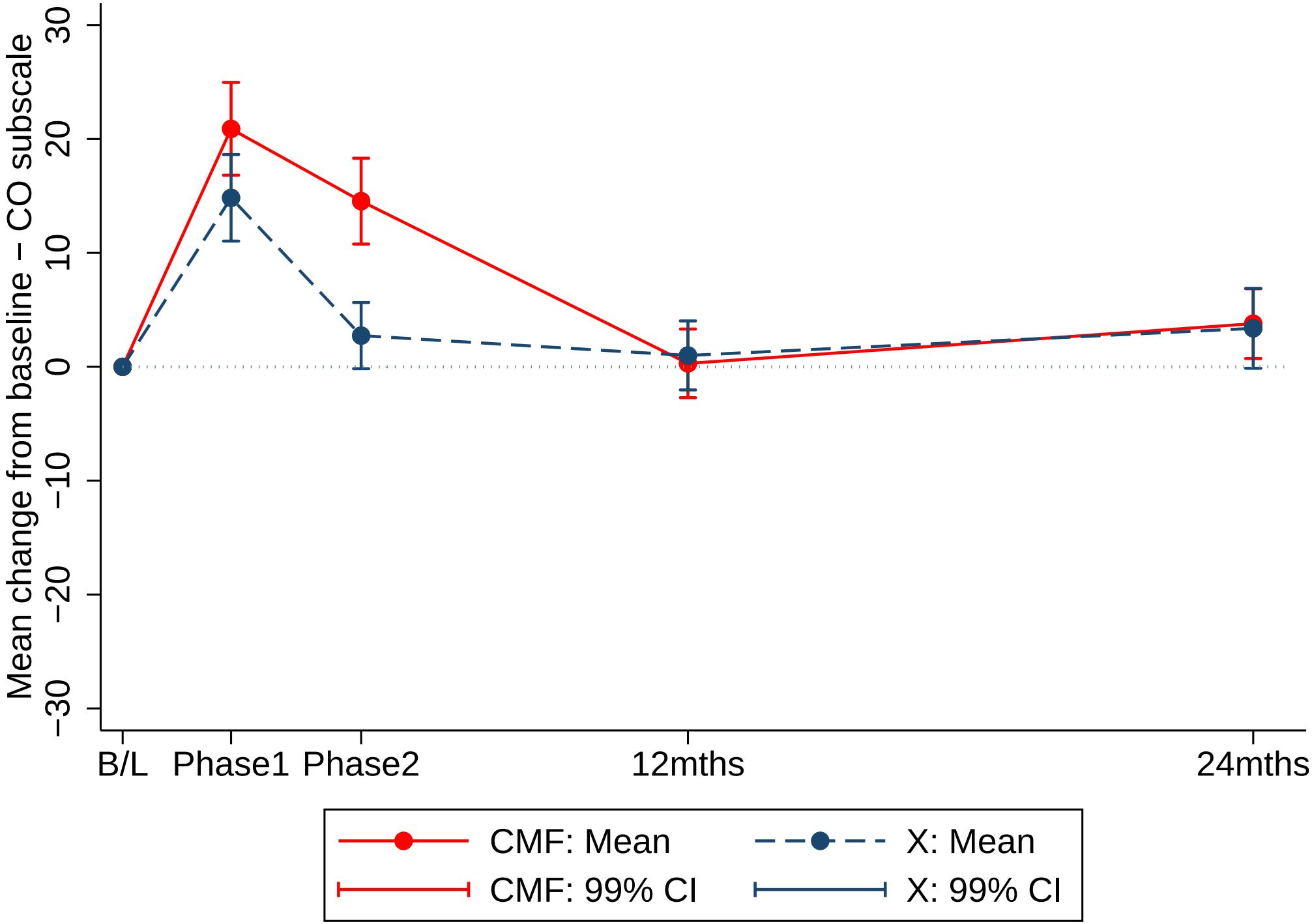

Mean change from baseline – FA subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

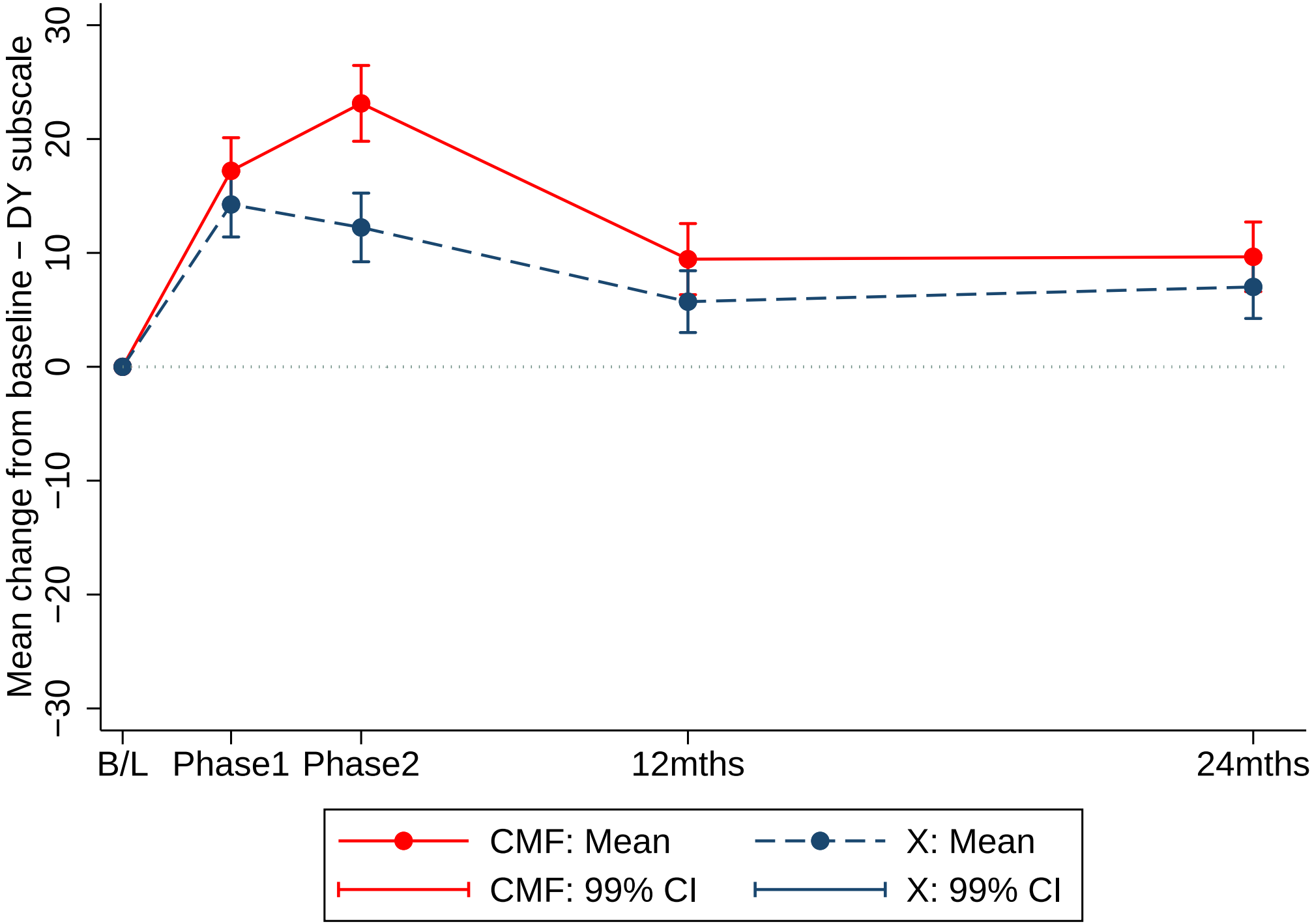

Mean change from baseline – BRCT subscale
−30
−20
−10
0
10
20
30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

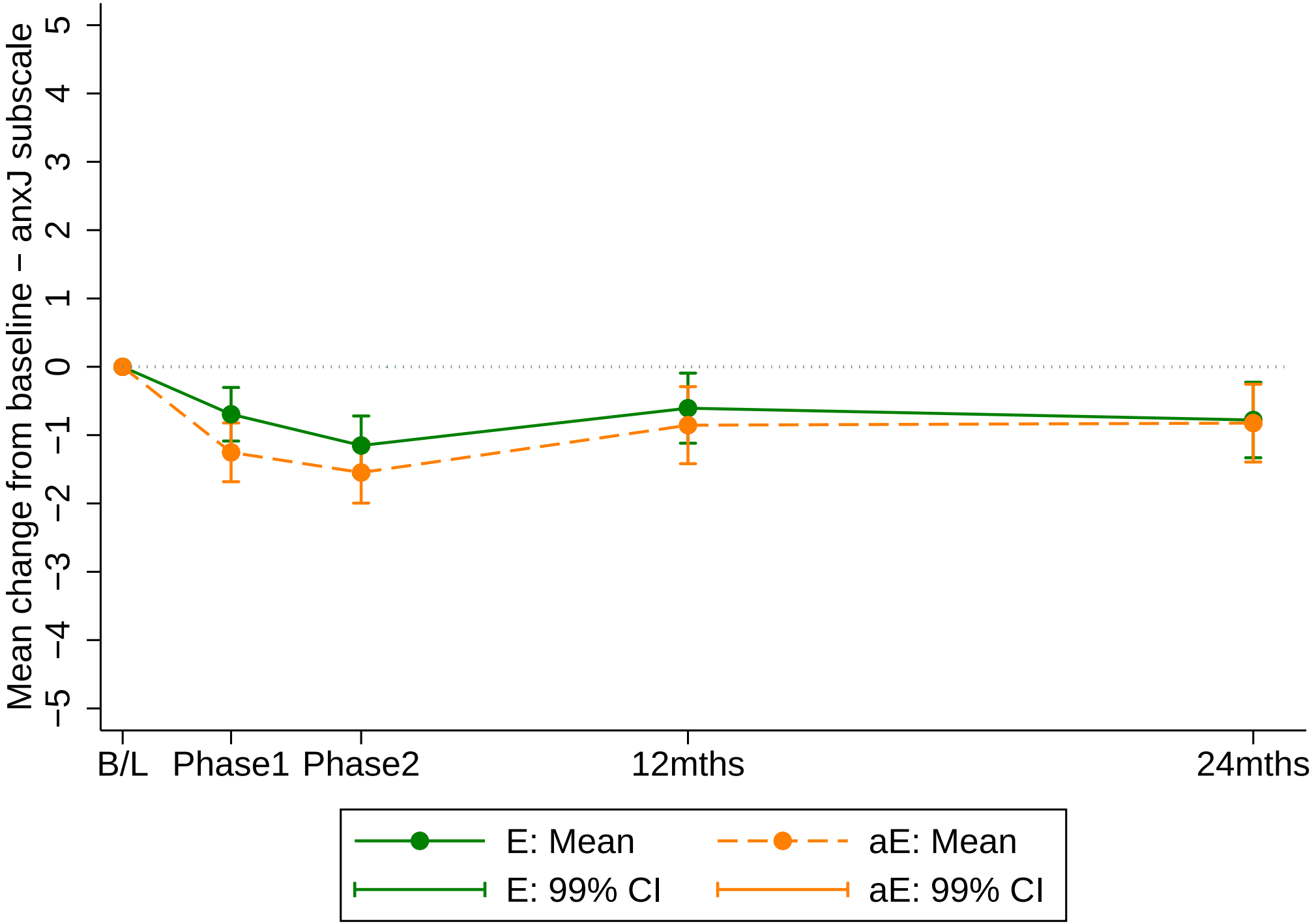

Mean change from baseline – BRSEF subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

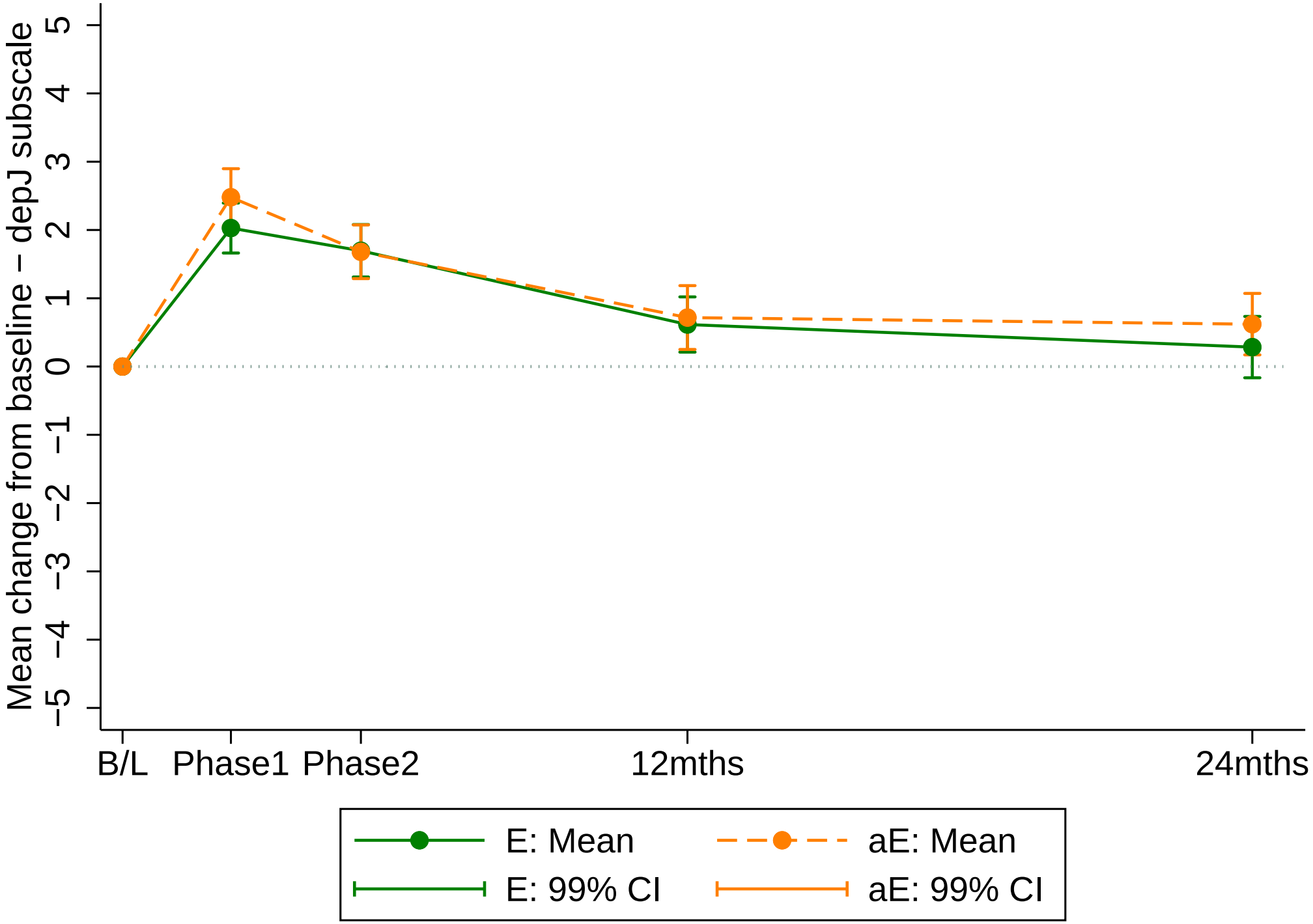

Mean change from baseline – SF subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

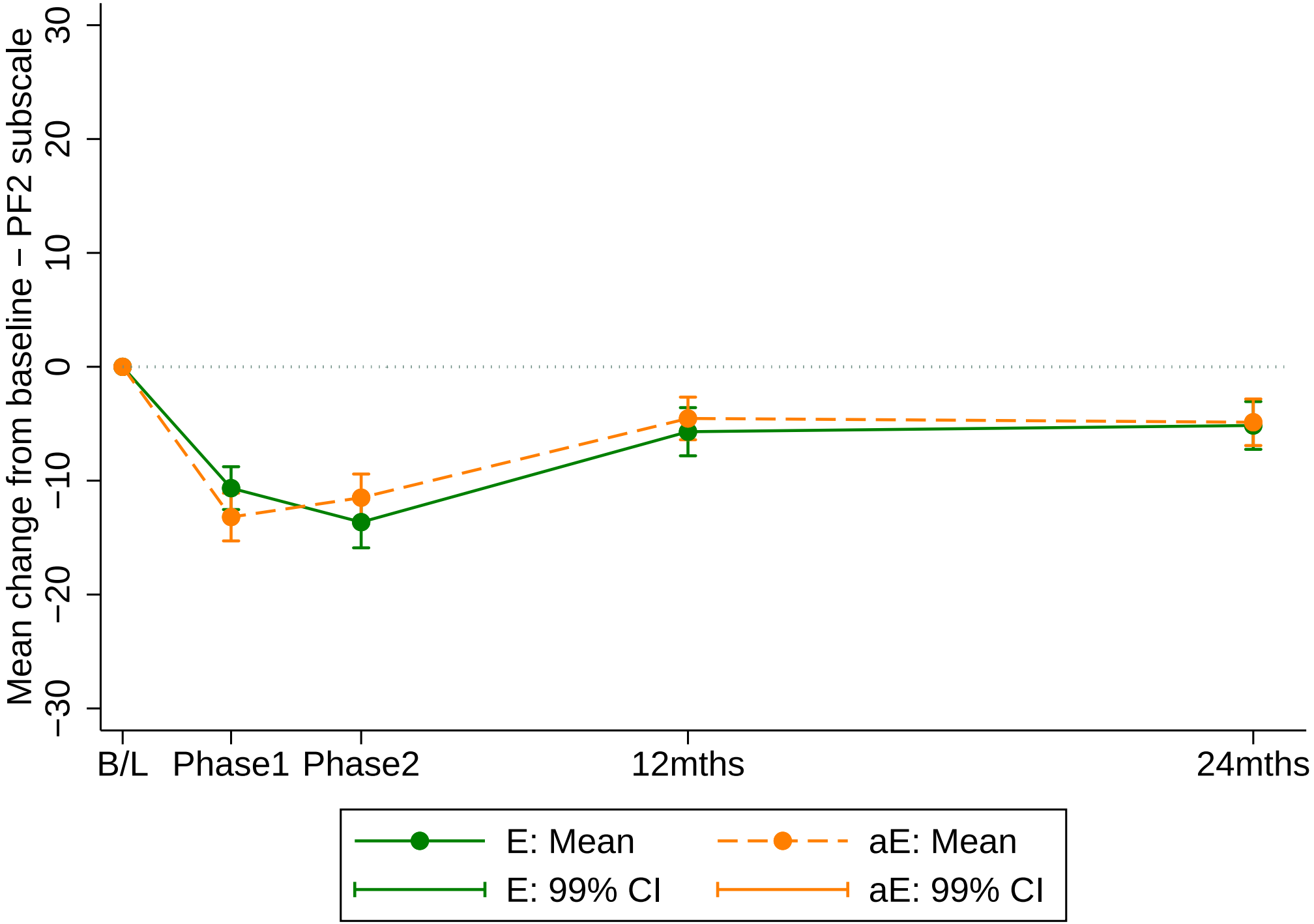

Mean change from baseline – PA subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

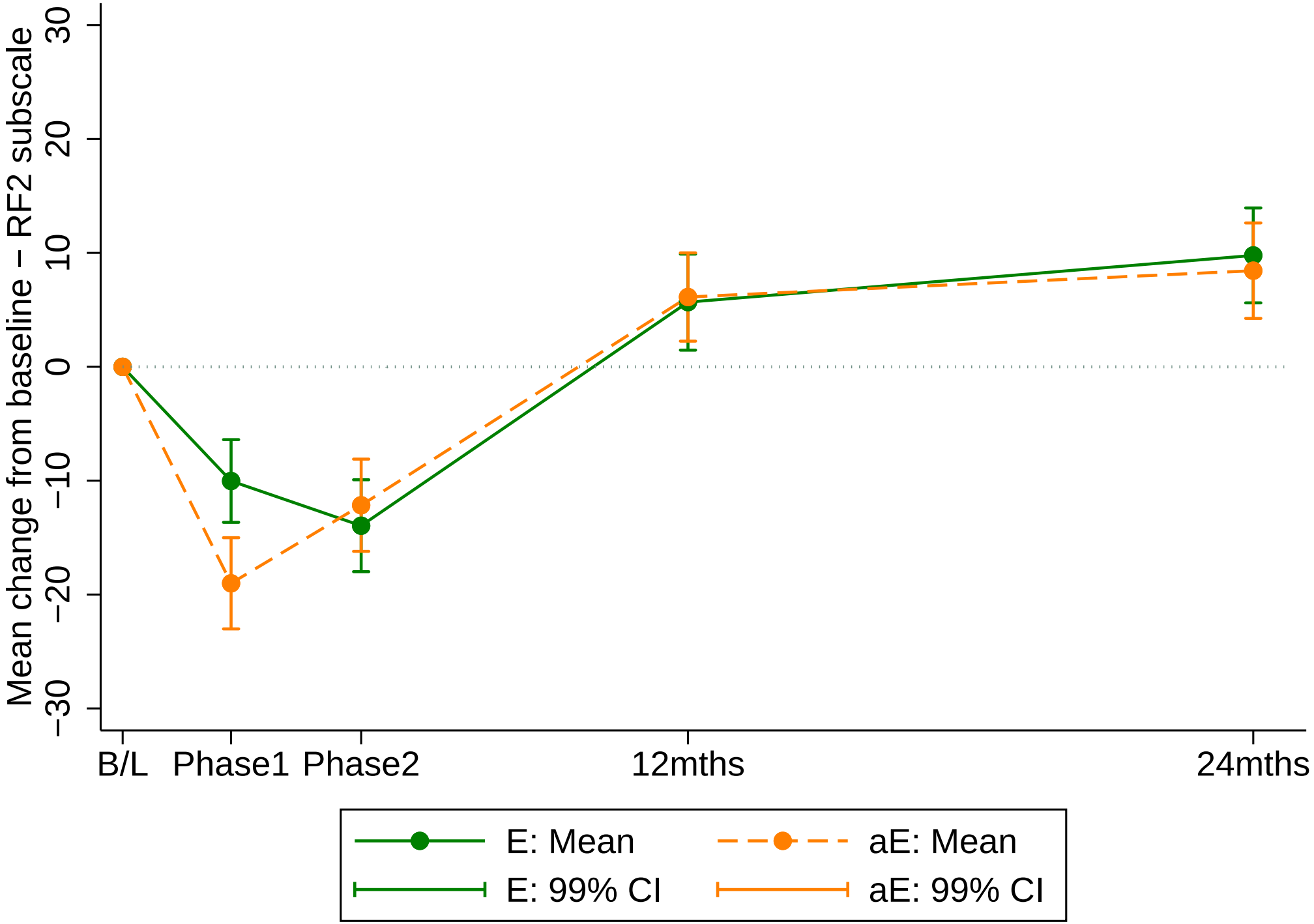

Mean change from baseline – CO subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

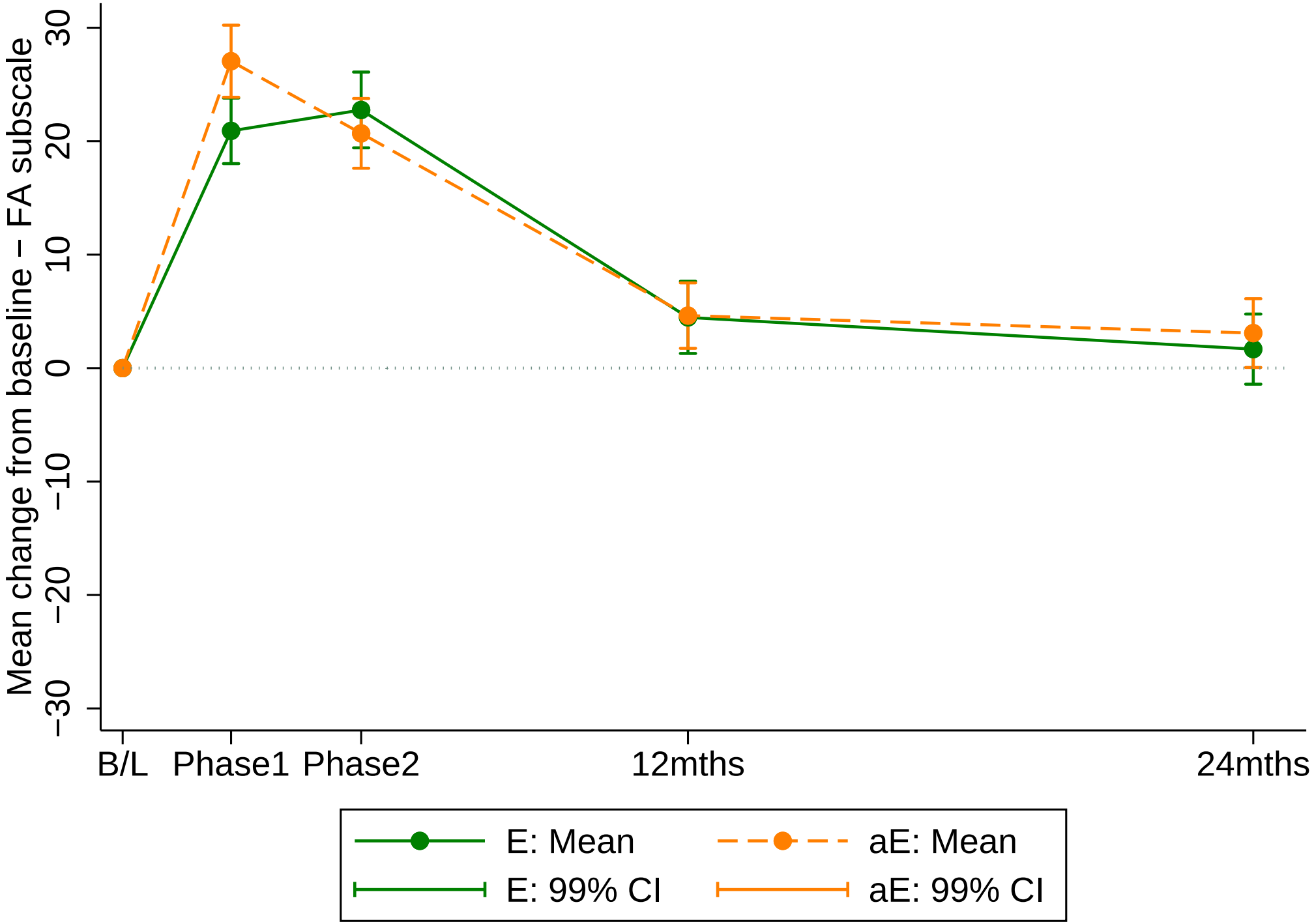

Mean change from baseline – DY subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI

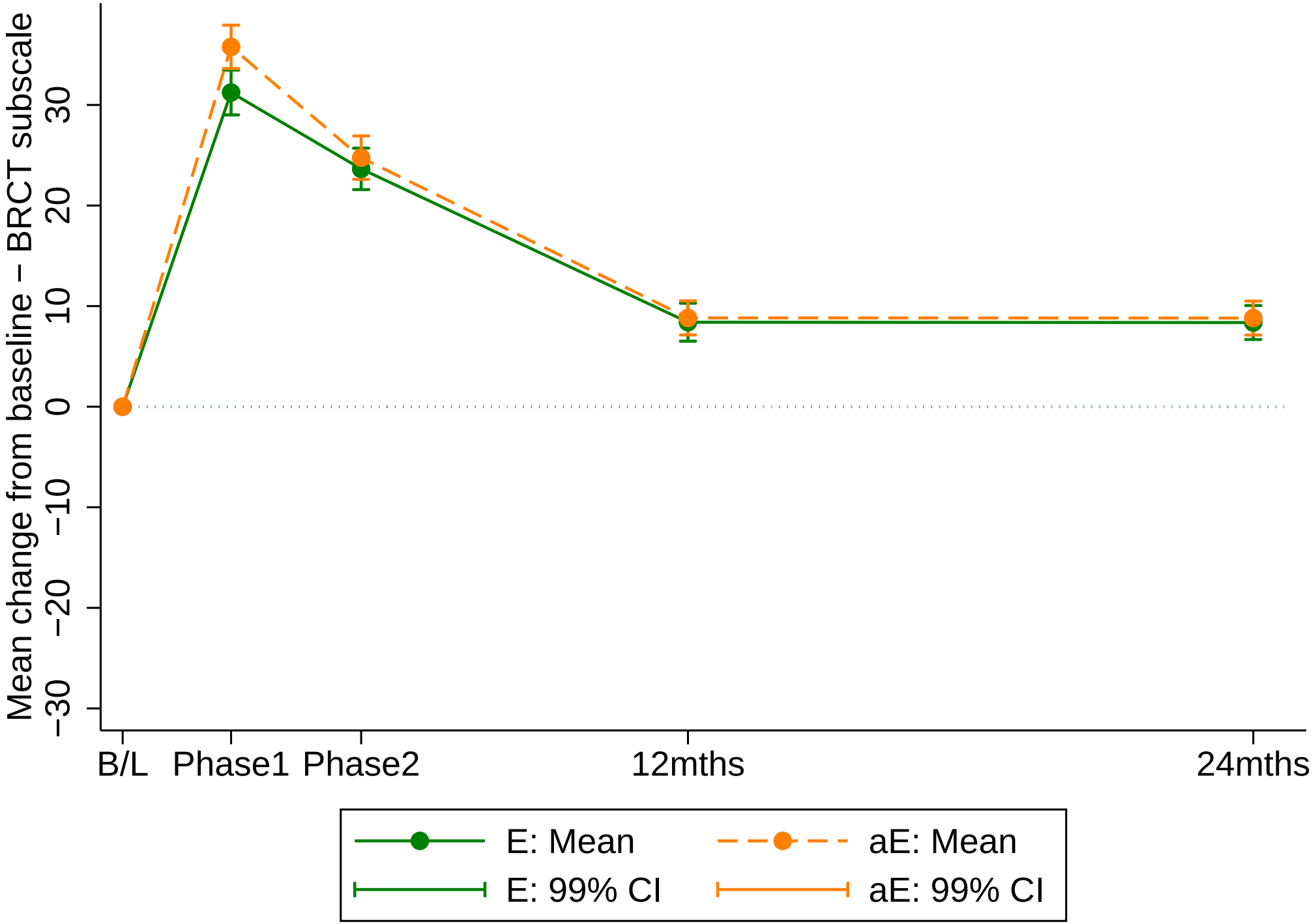

Mean change from baseline – anxJ subscale
5
4
3
2
1
0
−1
−2
−3
−4
−5
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

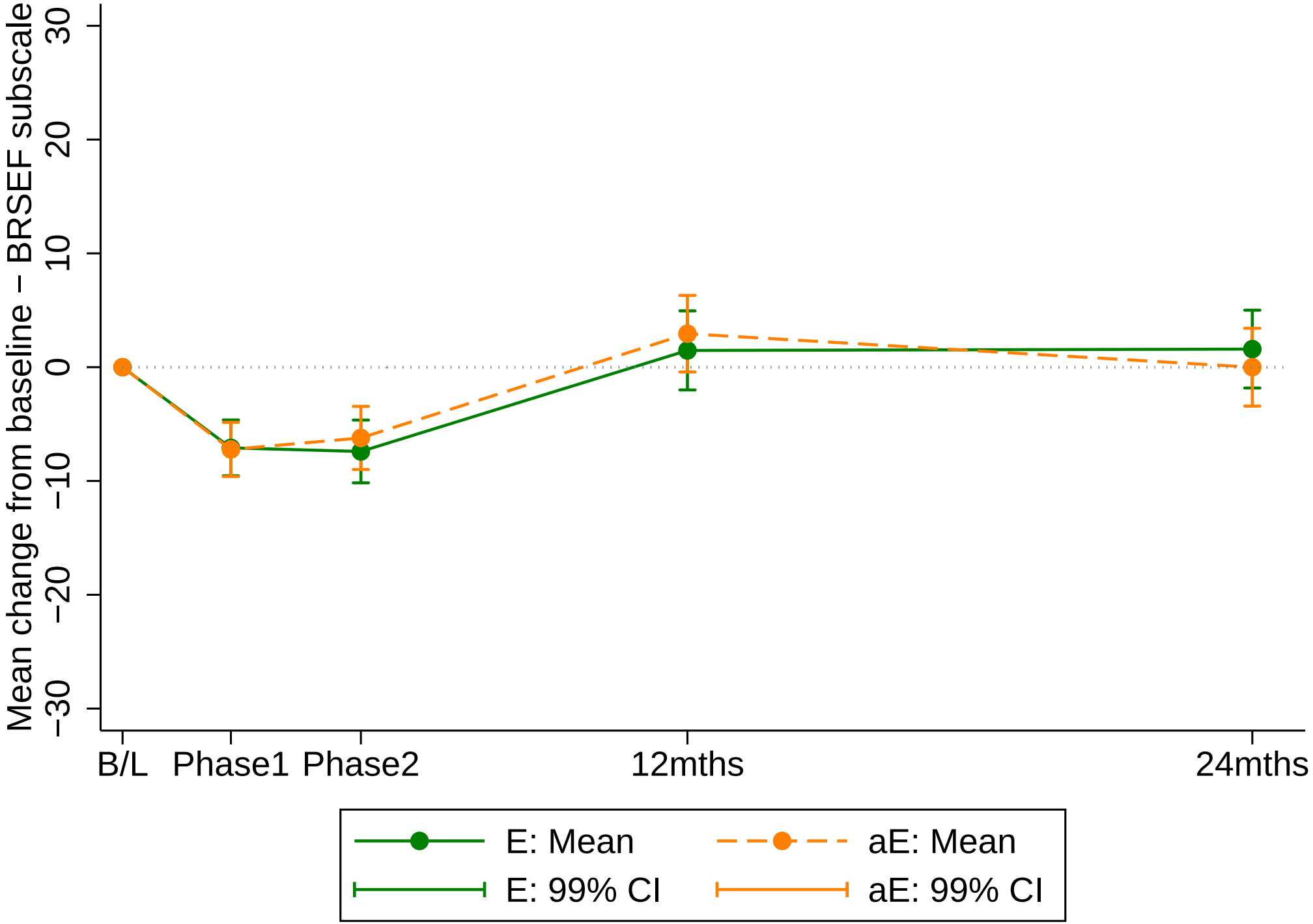

Mean change from baseline – depJ subscale
5
4
3
2
1
0
−1
−2
−3
−4
−5
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

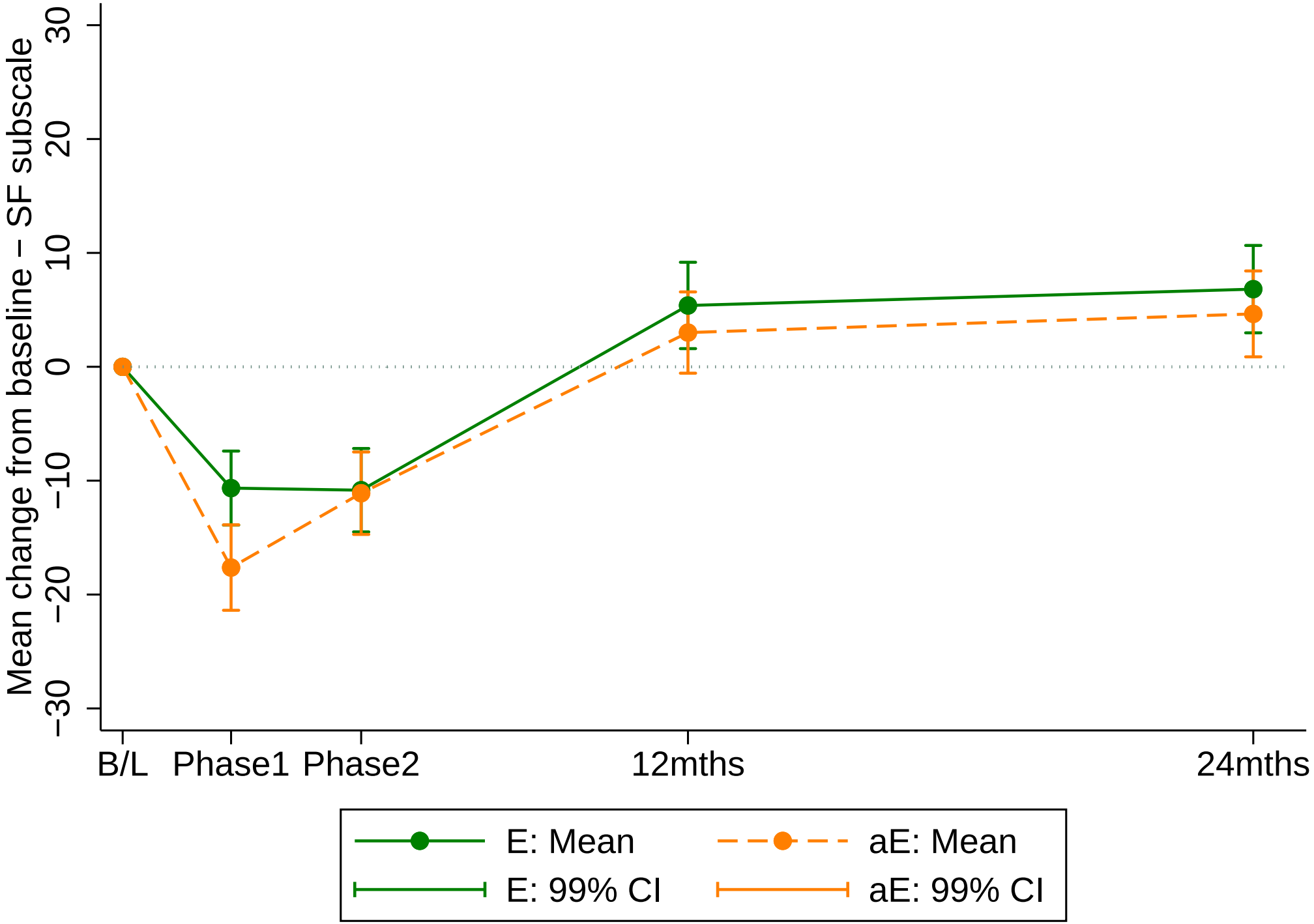

Mean change from baseline – PF2 subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

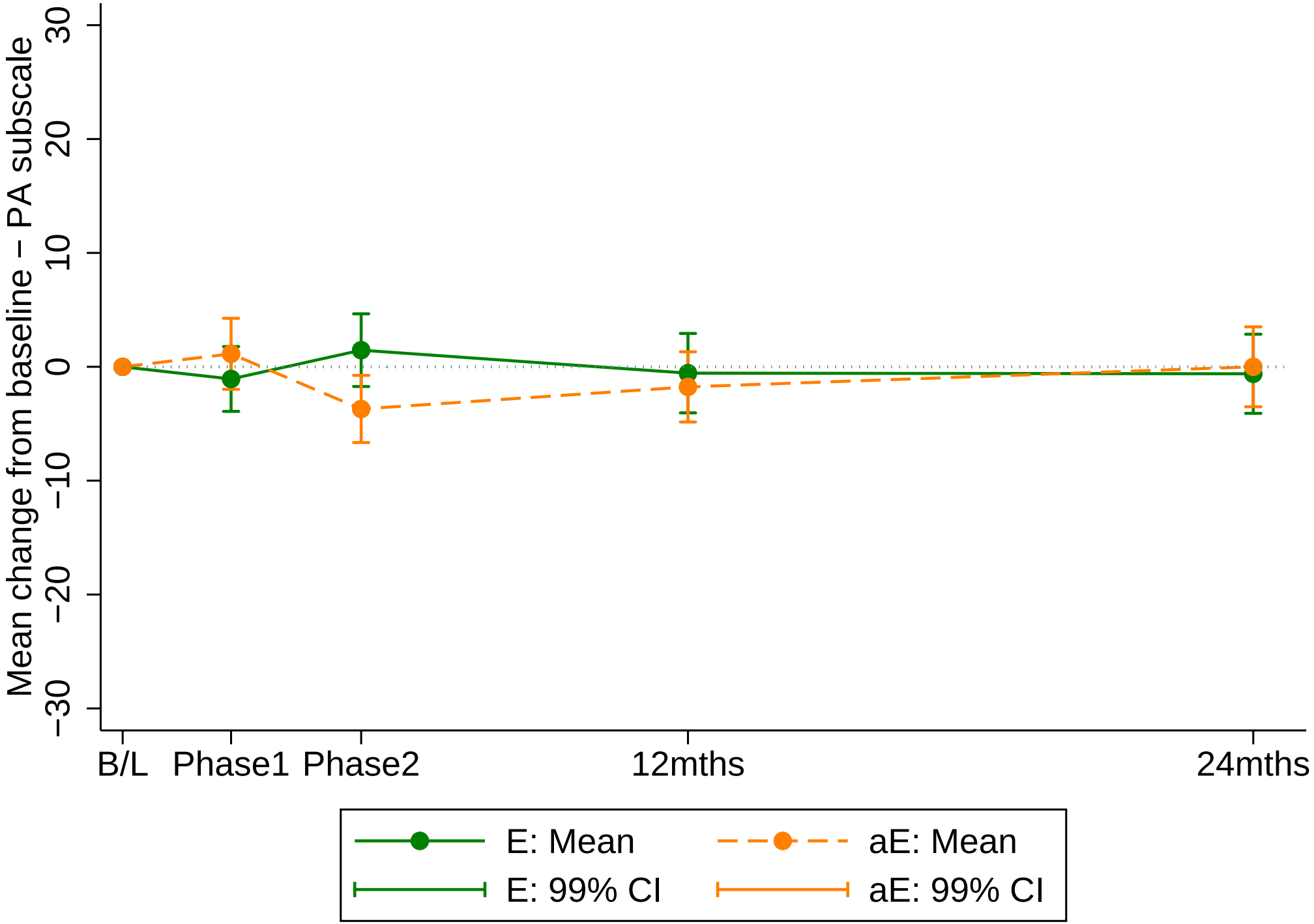

Mean change from baseline – RF2 subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

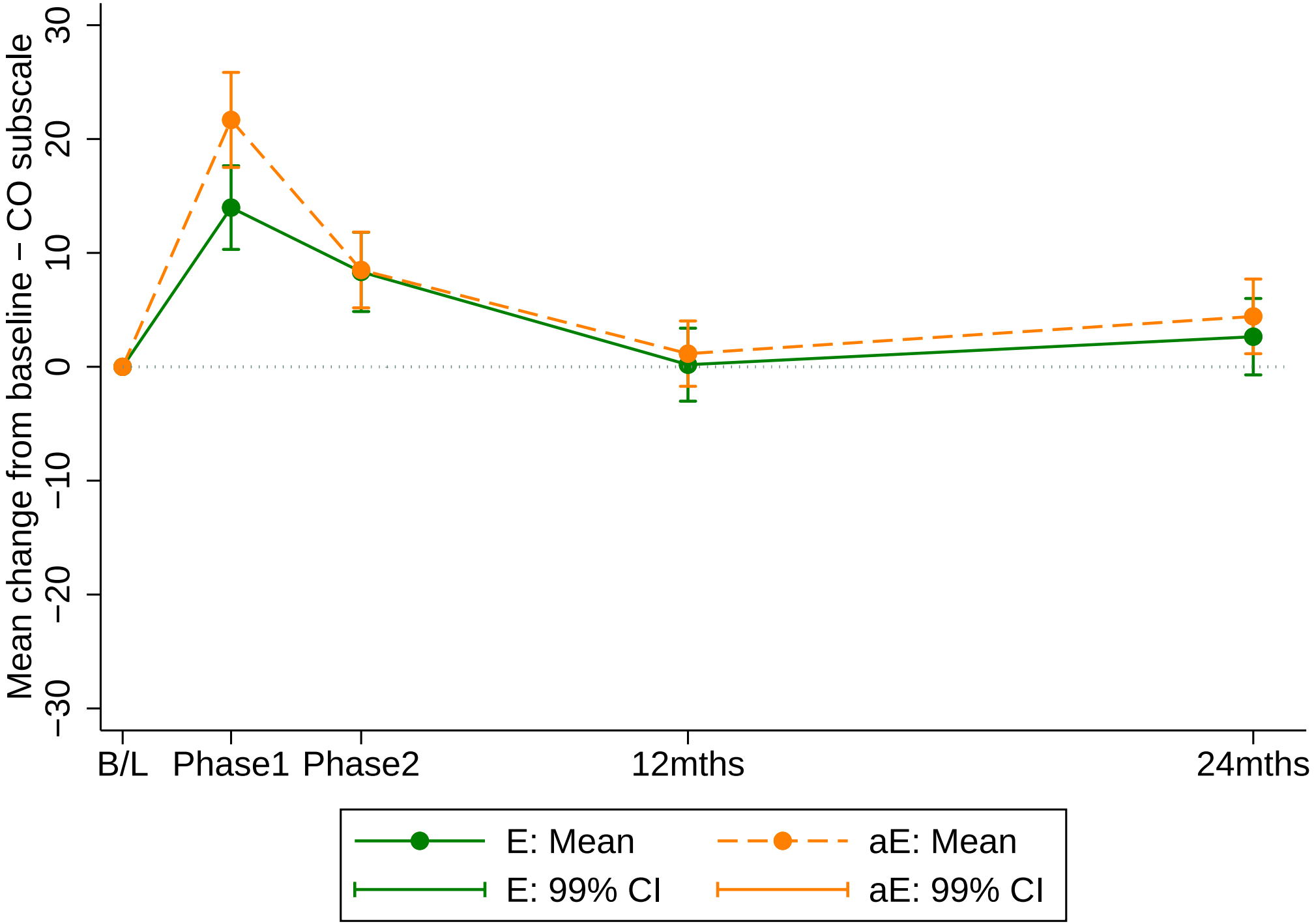

Mean change from baseline – FA subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

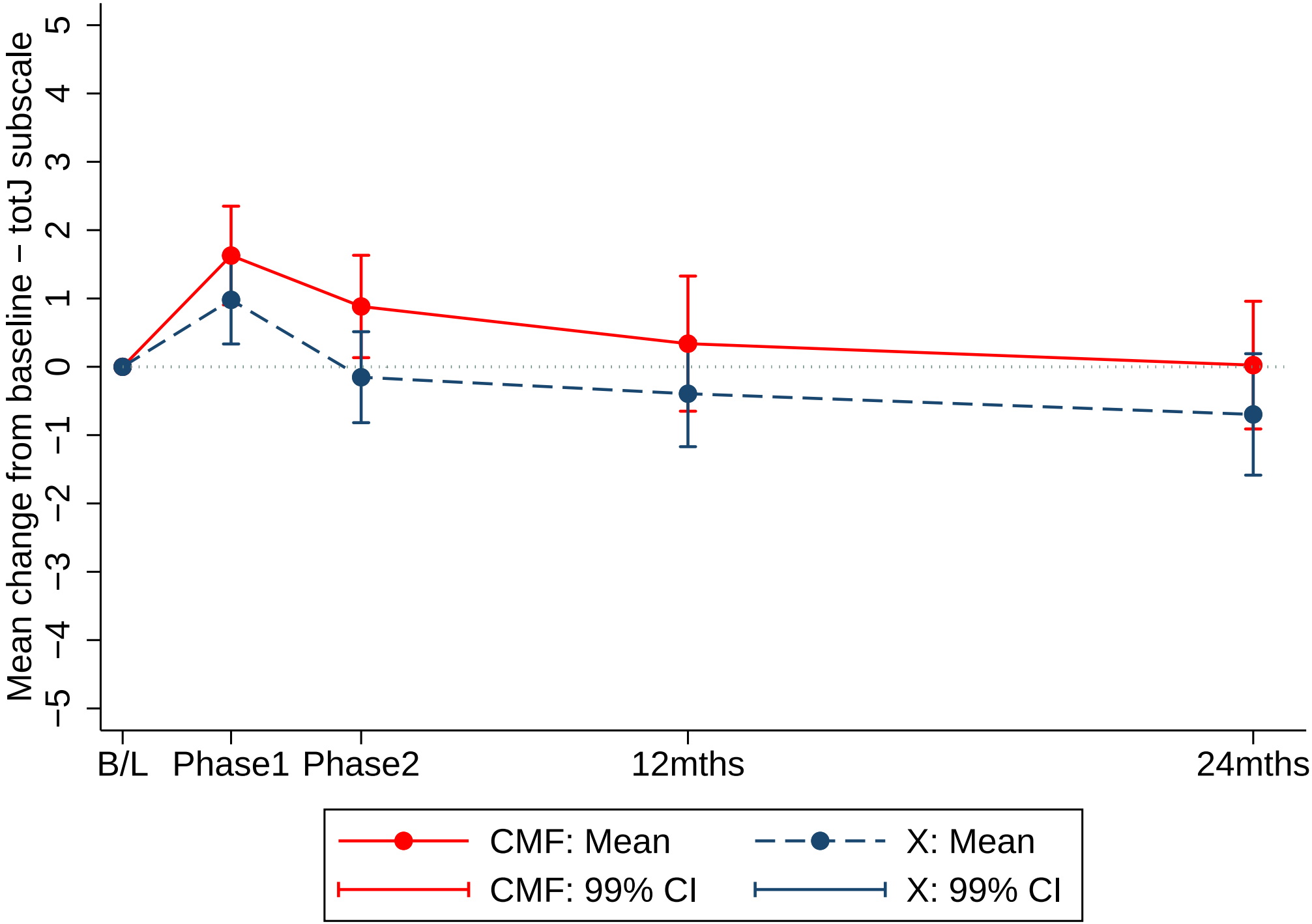

Mean change from baseline – BRCT subscale
−30
−20
−10
0
10
20
30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
E: 99% CI
aE: Mean
aE: 99% CI

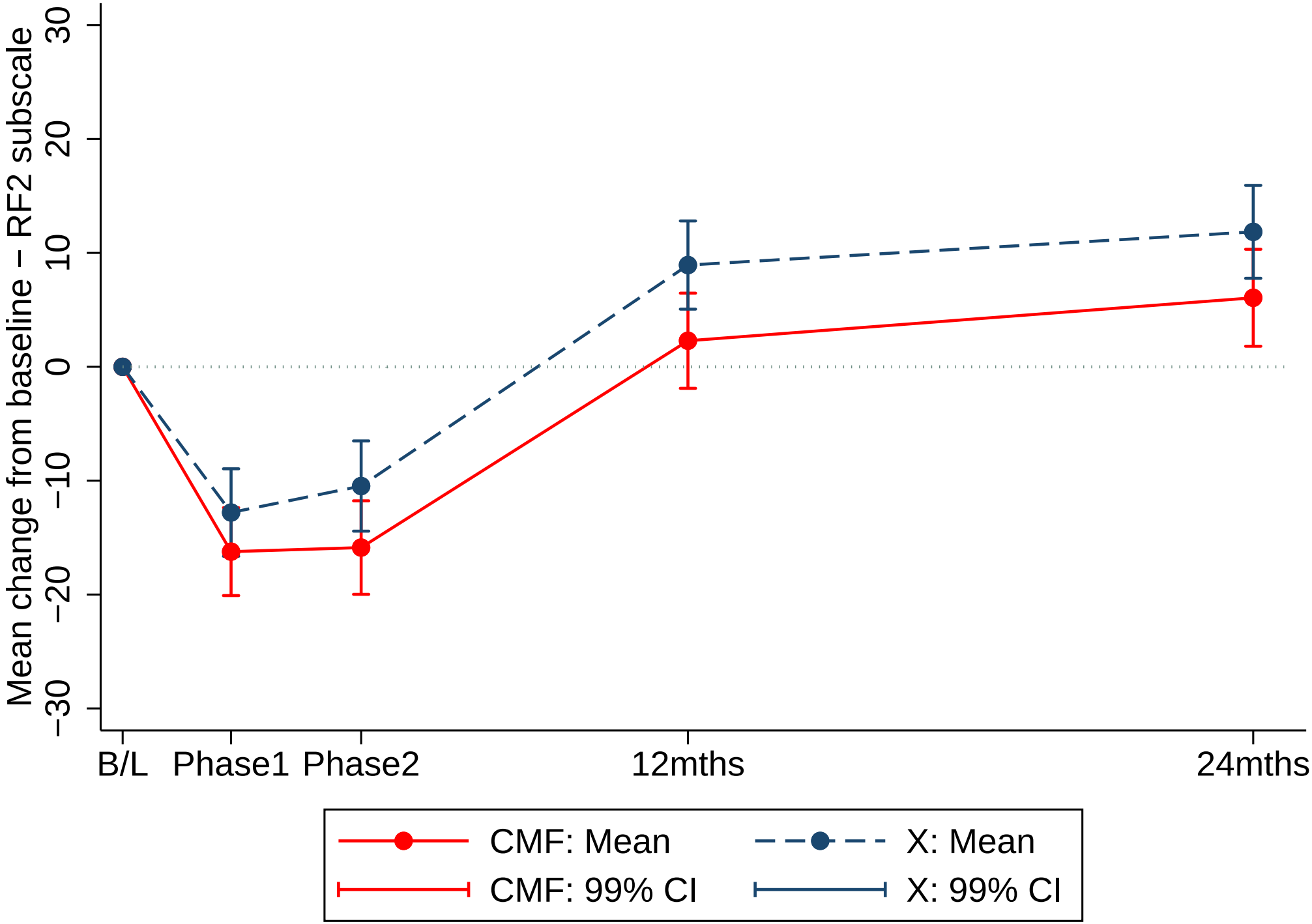

Mean change from baseline – BRSEF subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI

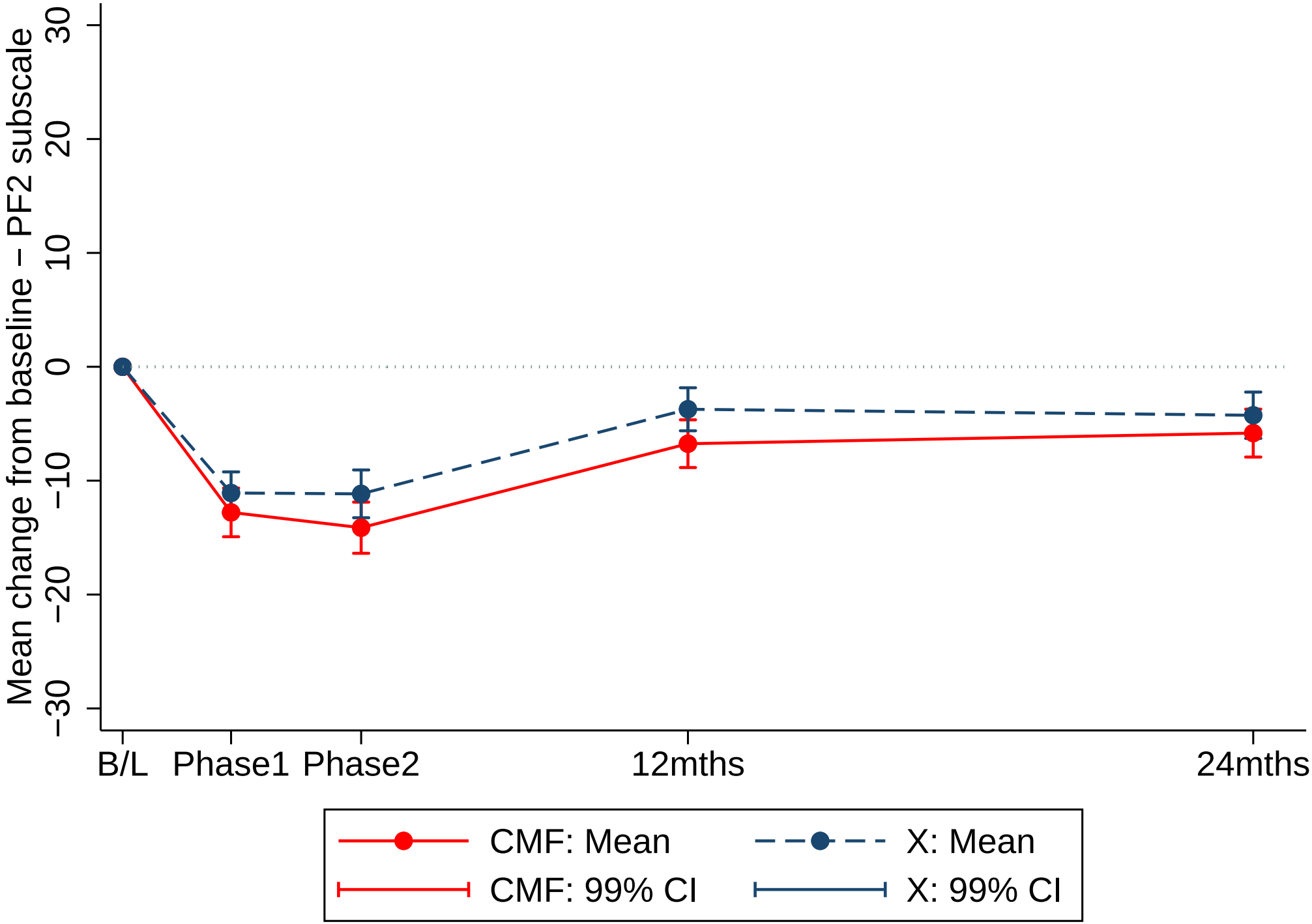

Mean change from baseline – SF subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI


Mean change from baseline – PA subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI


Mean change from baseline – CO subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
E: Mean
aE: Mean
E: 99% CI
aE: 99% CI


Mean change from baseline – totJ subscale
5
4
3
2
1
0
−1
−2
−3
−4
−5
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI


Mean change from baseline – RF2 subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI


Mean change from baseline – PF2 subscale
30
20
10
0
−10
−20
−30
B/L
Phase1
Phase2
12mths
24mths
CMF: Mean
X: Mean
CMF: 99% CI
X: 99% CI