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

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Summary

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

Methods TACT2 was a multicentre, phase 3, open-label, parallel-group, randomised, controlled trial done in 129 UK centres. Participants were aged 18 years or older with histologically confirmed node-positive or high-risk node-negative invasive primary breast cancer, who had undergone complete excision, and due to receive adjuvant chemotherapy. Patients were randomly assigned (1:1:1:1) 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 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 years *vs* >50 years), and planned endocrine treatment (yes *vs* no). QOL was one of the secondary outcomes and is reported here. All patients from a subset of 44 centres were invited to complete QOL questionnaires (Hospital Anxiety and Depression Scale [HADS] and European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire 30-item core module [QLQ-C30] and Quality of Life Questionnaire breast module [QLQ-BR23]) at baseline, end of standard or accelerated epirubicin, end of CMF or capecitabine, and at 12 and 24 months after randomisation. The QOL substudy prespecified two coprimary QOL outcomes assessed in the intention-to-treat population: overall QOL (reported elsewhere) and HADS total score. Prespecified secondary QOL outcomes were EORTC QLQ-C30 subscales of physical function, role function, and fatigue and EORTC QLQ-BR23 subscales of sexual function and systemic therapy side-effects. This trial is registered with ISRCTN, ISRCTN68068041, and ClinicalTrials.gov, NCT00301925.

Findings From Dec 16, 2005, to Dec 5, 2008, 4391 patients (20 [0·5%] of whom were male) were enrolled in TACT2; 1281 (85·8%) of 1493 eligible patients were included in the QOL substudy. Eight (0·6%) participants in the QOL substudy were male and 1273 (99·4%) were female. Median follow-up was 85·6 months (IQR 80·6–95·9). Analysis was performed on the complete QOL dataset (as of Sept 15, 2011) when all participants had passed the 24-month timepoint. Prerandomisation questionnaires were completed by 1172 (91·5%) patients and 1179 (92·0%) completed at least one postrandomisation questionnaire. End-of-treatment HADS depression score (p=0·0048) and HADS total change score (p=0·0093) were worse for CMF versus capecitabine. Accelerated epirubicin led to worse physical function (p=0·0065), role function (p<0·0001), fatigue (p=0·0002), and systemic side-effects (p=0·0001), but not sexual function (p=0·36), compared with standard epirubicin during treatment, but the effect did not persist. Worse physical function (p=0·0048), sexual function (p=0·0053), fatigue (p<0·0001), and systemic side-effects (p<0·0001), but not role functioning (p=0·013), were seen for CMF versus capecitabine at end of treatment; these differences persisted at 12 months and 24 months.

Lancet Oncol 2023

Published Online November 2, 2023 https://doi.org/10.1016/S1470-2045(23)00460-6

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See Online for appendix

Interpretation **Accelerated epirubicin was associated with worse QOL than was standard epirubicin but only during treatment. These findings will help patients and clinicians make an informed choice about accelerated chemotherapy. CMF had worse QOL effects than did capecitabine, which were persistent for 24 months. The favourable capecitabine QOL compared with CMF supports its use as an adjuvant option after neoadjuvant chemotherapy in patients with triple-negative breast cancer.**

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

Introduction

Improvements in outcomes for patients diagnosed with early breast cancer led to an increased emphasis on evaluating the toxicity of the adjuvant chemotherapy regimens and the longer-term effect on patients' health-related quality of life (QOL), especially when more

Research in context

Evidence before this study

At the time this study was designed in 2004, the optimal adjuvant chemotherapy treatment for patients with 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 patients with moderate risk early breast cancer was epirubicin 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. The TACT2 trial was designed to investigate whether use of accelerated epirubicin 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 effect on QOL. In 2003, a systematic review of health-related QOL measurement in patients with breast cancer identified only six randomised controlled trials of adjuvant chemotherapy in patients with breast cancer with QOL results, suggesting a transient negative effect, especially of more aggressive treatments (ie, anthracyclines and taxanes). An update of this systematic review in 2011 reported a 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, which showed worse psychological distress during dose-dense treatment with recovery by 6 months. One non-inferiority trial comparing classic CMF with an oral fluoropyrimidine (uracil–tegafur) showed similar efficacy but better QOL with oral chemotherapy. The TACT2 trial primary outcome showed no benefit for accelerated epirubicin 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. Accelerated epirubicin 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.

Added value of this study

Here, we report the results from the detailed TACT2 QOL substudy, 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. Our findings confirmed the negative effect of accelerated chemotherapy during treatment with additional information on the range of affected QOL areas (ie, physical and role functions, fatigue, and self-reported side-effects). To the best of our knowledge, for the first time we showed that this effect 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. 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 effect on QOL, and suggest that this additional burden resolves within 12 months of starting therapy. The lasting side-effects and functional effect of CMF adds to the clinical reasons for further reducing its use as part of adjuvant treatments for patients with early breast cancer. The favourable symptom burden and functions data on capecitabine supports its increased use as rescue adjuvant treatment after neoadjuvant chemotherapy with residual disease in patients with triple negative cancer.

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 whether to undergo adjuvant chemotherapy when the majority of patients would not individually benefit. For example, QOL results from the TACT trial[2] 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 by 2 years after treatment. Patient-reported data are acknowledged to have a key role in shared decision making about adjuvant chemotherapy.

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

TACT2[6] was a multicentre, phase 3, randomised controlled trial of adjuvant non-taxane chemotherapy in patients with early breast cancer, with a 2×2 factorial design. The control group received sequential epirubicin followed by cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy (based on NEAT trial[7] results). Two hypotheses were tested: (1) accelerating epirubicin 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. The primary outcome results showed no benefit for accelerating epirubicin and confirmed non-inferiority of capecitabine to CMF in time to tumour recurrence.[6] Only the primary QOL outcome (global health status/QOL scale) was reported in the primary publication.[6] The results confirmed better tolerability of capecitabine over CMF, with worse global QOL observed in patients on CMF at treatment end and the difference persisting at 12 months and 24 months, suggesting long-term negative effects of CMF. In the epirubicin and accelerated epirubicin comparison, global health status/QOL was worse with accelerated epirubicin during treatment, but did not persist afterwards. We aimed to identify the effect of the treatments on a wider range of patient symptoms and experiences (eg, psychological distress and 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 relevant to current clinical practice, because the 2019 meta-analysis[8] of dose-dense chemotherapy found only modest benefits (13% mortality reduction and 14% reduction in cancer recurrences). However, the short-term 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 decision making.[8] Furthermore, current practice includes the use of capecitabine as adjuvant therapy after neoadjuvant chemotherapy in patients with triple negative breast cancer who do not have a pathological complete response, for which there are few detailed QOL analyses.[9]

Here, we report the detailed TACT2 QOL substudy. We aimed to analyse all questionnaire data and build a comprehensive picture of patient experiences during chemotherapy and in the following 24 months. Our hypotheses were: (1) the more intense regimens (accelerating epirubicin and CMF) would result in worse patient-reported physical symptoms and greater effect on patient functioning in the end-of-treatment period; and (2) these differences would resolve by 12 months and 24 months.

Methods

Study design and participants

TACT2 was a multicentre, phase 3, open-label, parallel-group, randomised, controlled trial in patients with early breast cancer at 129 cancer centres and district general hospitals in the UK. The TACT2 study design has been described in detail elsewhere.[6] Eligible patients were women or men aged 18 years or older with histologically confirmed node-positive or high-risk node-negative 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 and 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. Participant sex data were collected from health records.

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

A 2×2 factorial design was used in which patients were randomly assigned (1:1:1:1) to receive either standard epirubicin followed by CMF, accelerated epirubicin followed by CMF, standard epirubicin followed by capecitabine, or accelerated epirubicin followed by capecitabine. The randomisation schedule was generated by computer at the Institute of Cancer Research Clinical Trials and Statistics Unit (London, UK). Randomisation was done via telephone by a research nurse to one of the

four participating clinical trials units: Clinical Trials and Statistics Unit at The Institute of Cancer Research (which had overall responsibility for trial coordination); Cancer Clinical Trials Unit, Edinburgh, UK; Leeds Clinical Trials Research Unit, Leeds, UK; and the Cancer Research UK Clinical Trials Unit, Birmingham, UK. Computer-generated permuted blocks of sizes 8 and 12 were used. Stratification was by centre, number of nodes involved (0 *vs* 1–3 *vs* ≥4), age (≤50 years *vs* >50 years), and planned endocrine treatment (yes *vs* no).

Procedures

Patients received either four cycles of intravenous epirubicin (100 mg/m²) once every 3 weeks (standard epirubicin) or once every 2 weeks plus 6 mg pegfilgrastim on day 2 of each cycle (accelerated epirubicin); followed by four cycles of either CMF every 4 weeks (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; and 600 mg/m² fluorouracil intravenously days 1 and 8) or four 3-week cycles of 2500 mg/m² capecitabine (1250 mg/m² given orally twice daily on days 1–14 of each cycle). All patients were followed up at 12 months, 18 months, and 24 months, then yearly for at least 10 years after randomisation.

The QOL and toxicity substudy was done in 44 of the participating centres (appendix pp 3–4). All patients in the substudy 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 and before random assignment. Subsequent questionnaires were sent by post by the QOL substudy coordinator (at Cancer Clinical Trials Unit, Edinburgh,UK). The timepoints for QOL questionnaires were selected to allow measurement immediately after epirubicin or accelerated epirubicin and CMF or capecitabine (for acute effects), and 12 months and 24 months after random assignment (for late effects). In the first protocol version, the timing of assessments included a 6-week assessment during epirubicin or accelerated epirubicin but this was unfeasible in practice. The QOL data collection was temporarily suspended and the schedule was simplified (protocol version 2: Sept 1, 2007). We refer to those two periods of QOL data collection as stages QL1 and QL2 (appendix pp 4–6).

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

We also used the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire 30-item core module (QLQ-C30; version 3.0) and breast module (QLQ-BR23; version 1.0). The EORTC QLQ-C30 measures health-related QOL of patients with cancer in general, supplemented by cancer site-specific modules. EORTC QLQ-C30 has 30 questions addressing five functional scales (ie, physical, role, social, emotional, and cognitive), one global health status/QOL scale, three symptom scales (ie, fatigue, nausea or vomiting, and pain), five symptom items (ie, appetite loss, constipation, diarrhoea, dyspnoea, and insomnia), and one financial difficulties item.[11] The EORTC QLQ-BR23 focuses on issues specific to breast cancer, and has 23 questions with four functional scales (ie, body image, future perspective, sexual enjoyment, and sexual functioning) and four symptom scales (ie, arm symptoms [swelling in arm or hand, arm or shoulder pain, and difficulty raising the arm], breast or chest wall symptoms [pain, swelling, oversensitivity, and skin problems in the area of the affected breast], and systemic therapy side-effects [dry mouth, taste changes, sore eyes, hair loss, feeling ill, hot flashes, headaches, and upset by hair loss]).[12] All scores for the EORTC QLQ-C30 and 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 global health status/QOL scale represent a superior level of functioning or better QOL, whereas higher scores in the symptom scales represent worse symptoms.

Outcomes

The protocol-specified coprimary QOL outcomes were overall QOL (EORTC QLQ-C30 global health status/QOL subscale) and HADS total score at the end of treatment, at 12 months, and at 24 months. EORTC QLQ-C30 global health status/QOL subscale results have been published elsewhere, along with the patient-reported chemotherapy-specific toxicities during treatment.[6] Here we report the analysis of HADS and the prespecified secondary QOL outcomes of interest: the EORTC QLQ-C30 subscales of physical function, role function, and fatigue and the EORTC QLQ-BR23 subscales of sexual function and systemic therapy side-effects at the end of epirubicin or accelerated epirubicin, at the end of CMF or capecitabine, and at 12 months and 24 months.

Exploratory analysis of the remaining subscales and items (EORTC QLQ-C30 social, emotional, cognitive function, pain, nausea and vomiting, appetite loss, constipation, diarrhoea, dyspnoea, insomnia, and financial difficulties; EORTC QLQ-BR23 body image, sexual enjoyment, future perspective, breast and chest wall symptoms, arm symptoms, and hair loss) was performed, which included descriptive analysis at baseline and each timepoint (end of epirubicin and accelerated epirubicin, end of CMF and capecitabine treatment, 12 months, and 24 months), cross-sectional analysis of the differences between the two treatments

(epirubicin *vs* accelerated epirubicin and CMF *vs* capecitabine) using Mann-Whitney non-parametric tests, and between-group comparisons of change in QOL scores (QOL score at each timepoint minus baseline score) using analysis of covariance adjusting for baseline score.

Statistical analysis

The QOL substudy aimed to include 1000 patients to provide complete case data on 800–850 patients, assuming 15–20% attrition at 12 months (based on the TACT trial[2]). If there was a carry-over effect between the treatments, looking at four separate groups of

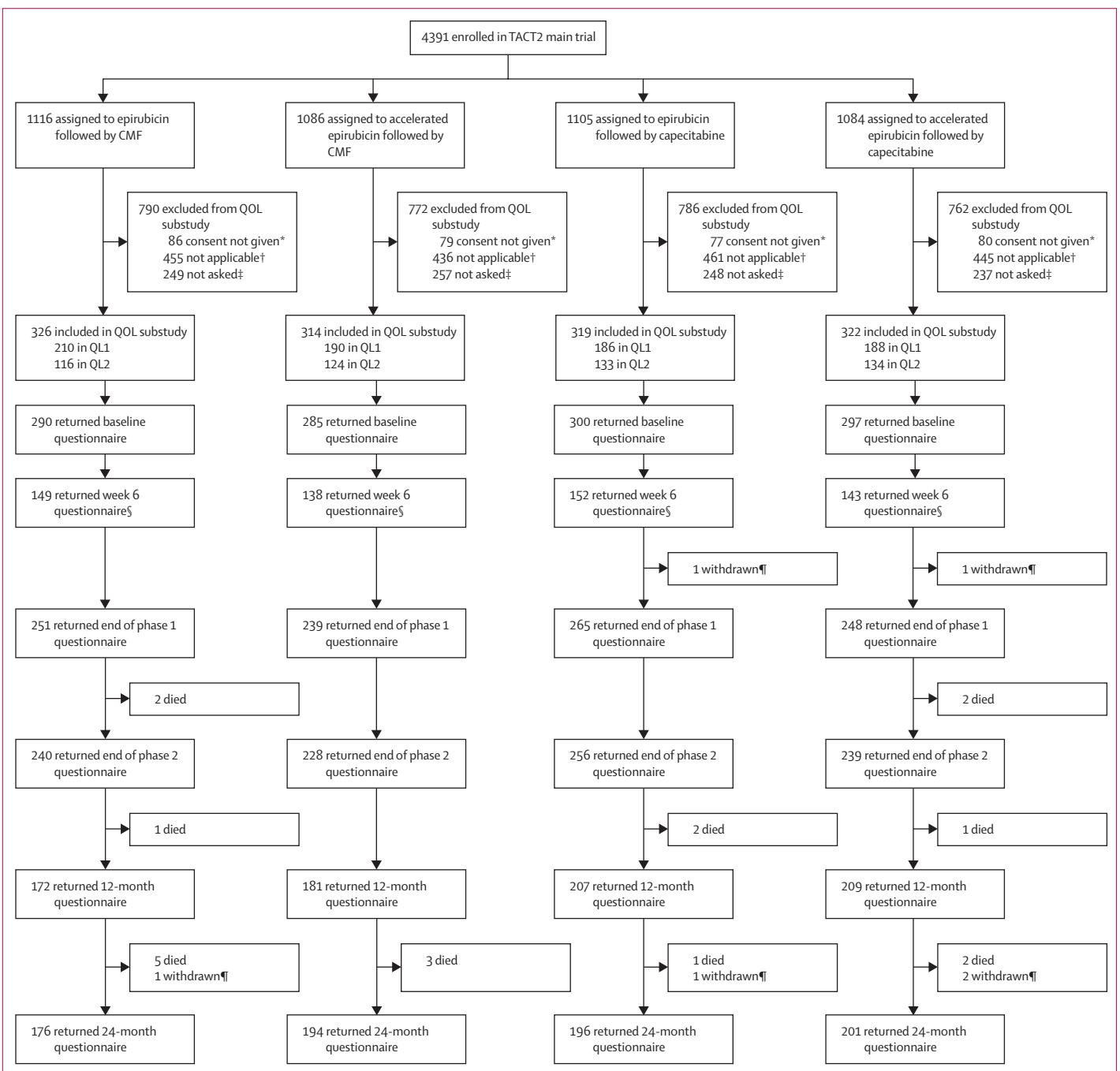


Figure 1: **Trial profile**

CMF=cyclophosphamide, methotrexate, and fluorouracil. QL1=data collection period 1. QL2=data collection period 2. QOL=quality of life. *Consent not given: patients were approached for the QOL substudy but declined participation. †Not applicable: patients from centres not participating in the QOL substudy. ‡Not asked: patients in a QOL substudy-participating centre but recruited during the pause between QL1 and QL2. §Week 6 questionnaire was only sent to patients in QL1. ¶All withdrawn due to patient request, except one who moved abroad.

200–213 patients at the 12-month assessment would provide 92–94% power to detect a difference of 20% or more (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. Although for the main trial we did not expect an interaction between the treatment groups, we could not presume that for QOL outcomes, so the QOL substudy was powered for four-group comparison. For the comparison between CMF and capecitabine, we had an a priori hypothesis expecting a better QOL in the capecitabine group, whereas for epirubicin versus accelerated epirubicin, we did not have an a priori hypothesis regarding QOL. Mean differences of 5 points or more at the group level in scores between the epirubicin followed by CMF group and the other treatment groups were considered clinically relevant. A 5-point mean difference with SD of 19 (as shown in the TACT trial[2]) 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 or more with 90% power or greater (α=0·01).

QOL data at baseline and each timepoint (end of epirubicin and accelerated epirubicin, end of CMF and capecitabine treatment, 12 months, and 24 months) were analysed descriptively using the subscale and item scores. Cross-sectional analysis of the differences between the two treatments (epirubicin *vs* accelerated epirubicin and CMF *vs* capecitabine) was done with Mann-Whitney non-parametric tests. Analyses of change in QOL scores (QOL score at each timepoint minus baseline score) were compared between groups using analysis of covariance adjusting for baseline score. The mean change from baseline to each timepoint with 99% CIs was plotted by treatment group.

Using an approach known as responder analysis, recommended by the US Food and Drug Administration, we evaluated if the observed significant differences in changes in scores on a treatment group level were clinically meaningful at the individual level.[14] Changes in 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 cutoff means a change of at least one response category—eg, from not at all to a little).[15] We only assessed 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 were 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 a clinical audience and enable visual presentation of the multiple QOL domains by study group.

Generalised estimating equation models were used to analyse the data longitudinally across all timepoints, including covariates for randomly assigned treatments (epirubicin *vs* accelerated epirubicin and CMF *vs* capecitabine), baseline score, time from baseline to follow-up questionnaire completion, QOL study stage (QL1 or QL2), age at randomisation, and type of surgery

	Patients consenting to QOL study (n=1281)	Patients not participating in QOL study (n=3110)
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		
Premenopausal	482 (37·6%)	1178 (37·9%)
Postmenopausal	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%)
Oestrogen receptor and progesterone receptor status		
Oestrogen receptor positive and progesterone receptor positive	564 (44·0%)	1476 (47·5%)
Oestrogen receptor positive and progesterone receptor negative	101 (7·9%)	275 (8·8%)
Oestrogen receptor positive and progesterone receptor unknown*	289 (22·6%)	459 (14·8%)
Oestrogen receptor negative and progesterone receptor positive	15 (1·2%)	34 (1·1%)
Oestrogen receptor negative and progesterone receptor negative	292 (22·8%)	807 (25·9%)
Oestrogen receptor negative and progesterone receptor 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		
Oestrogen receptor positive or progesterone receptor positive (or both) and HER2 negative (luminal)	782 (61·0%)	1884 (60·6%)
HER2 positive, oestrogen receptor positive, or progesterone receptor positive	176 (13·7%)	351 (11·3%)
HER2 positive, oestrogen receptor negative, and progesterone receptor negative	89 (6·9%)	215 (6·9%)
Triple negative	221 (17·3%)	648 (20·8%)
Not known	13 (1·0%)	12 (0·4%)

(Table 1 continues on next page)

(wide local excision or mastectomy). For each model, the following terms were included if found to improve the model fit: interaction between randomly assigned treatment group and timing of questionnaire (to account for the possibility of treatment effects not being constant across time); and interaction between randomly assigned phase 1 (epirubicin or accelerated epirubicin) and phase 2 (CMF or capecitabine) treatments. An unstructured correlation matrix and robust standard errors were used for all models.

A post-hoc exploratory subgroup analysis of patients' menopausal status at 18 months was done for the prespecified QOL subscales scores at 24 months. Three groups of patients were compared: premenopausal at baseline remaining premenopausal at 18 months, premenopausal at baseline and postmenopausal at 18 months, and postmenopausal at baseline. The analyses were performed for physical and role functioning, fatigue, sexual function, and systemic side effects, using *t*-tests and Mann-Whitney non-parametric tests. In addition, adjusted analyses employed regression models with QOL scales score as the outcome and the following as model covariates: menopausal status subgroup, endocrine treatment planned (none, tamoxifen, tamoxifen followed by aromatase inhibitor, aromatase inhibitor), and oestrogen and progesterone receptor status. Another post-hoc exploratory analysis was done to investigate whether there was an association between dyspnoea (patient-reported) and anaemia (Common Terminology Criteria for Adverse Events grades), using descriptive statistics and tabulations at the end of phase 2 treatment.

Statistical analysis was done on an intention-to-treat basis, including all patients who completed their prerandomisation questionnaire and at least one postrandomisation questionnaire. For all statistical comparisons, a significance level of 0·01 was used with associated 99% CIs 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 effect of the change of timings of assessments between the first (QL1) and second (QL2) stages of recruitment into the QOL substudy was done. Analyses of the change in QOL from baseline to the end of phase 2 treatment were repeated separately for QL1 and QL2 patients for all QLQ-C30, QLQ-BR23, and HADS subscale scores.

A database snapshot was taken on Aug 25, 2015. All analyses were performed using STATA version 13 or higher. This study is registered with ISRCTN, ISRCTN68068041, and ClinicalTrials.gov, NCT00301925.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Patients consenting to QOL study (n=1281)	Patients not participating in QOL study (n=3110)
(Continued from previous page)		
Histological type		
Infiltrating ductal	1074 (83·8%)	2586 (83·2%)
Infiltrating lobular	113 (8·8%)	287 (9·2%)
Mixed ductal or lobular	48 (3·7%)	103 (3·3%)
Other	46 (3·6%)	134 (4·3%)
Tumour size, cm		
≤2	526 (41·1%)	1276 (41·0%)
>2 and ≤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%)

QOL=quality of life. *Oestrogen receptor status and nodal involvement not known for one patient, assumed to be have been oestrogen receptor positive and to have had zero nodes involved based on their stratification at randomisation. †Includes patients who had both a wide local excision and mastectomy.

Table 1: **Baseline characteristics for participants in the QOL substudy and all TACT2 participants excluded from QOL substudy**

Results

From Dec 16, 2005, to Dec 5, 2008, 4391 patients (20 [0·5%] of whom were male) were enrolled in the TACT2 trial. 1281 (85·8%) of 1493 eligible patients from 44 centres participated in the QOL substudy (figure 1). Eight (0·6%) participants in the QOL substudy were male and 1273 (99·4%) were female (table 1). Median follow-up was 85·6 months (IQR 80·6–95·9). Analysis was performed on the complete QOL dataset (as of Sept 15, 2011) when all participants had passed the 24 month timepoint. Prerandomisation baseline questionnaires were completed by 1172 (91·5%) participants and 1179 (92·0%) participants completed at least one post-randomisation questionnaire. Compliance rates with questionnaire returns were between 73·8% and 83·3% during the treatment, and 52·9% and 65·7% at 12 and 24 months. Completion rates were similar across treatment groups except that there was a lower compliance rate at 12 and 24 months in the group who received epirubicin followed by CMF (appendix pp 7–8). No differences were found by type of surgery and nodal status, but the proportion of patients who completed a 24-month questionnaire was lower among premenopausal patients

	Standard epirubicin followed by CMF (n=290)	Accelerated epirubicin followed by CMF (n=285)	Standard epirubicin followed by capecitabine (n=300)	Accelerated epirubicin followed by capecitabine (n=297)
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 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%)	273 (100%)	290 (100%)	286 (100%)
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%)	273 (100%)	290 (100%)	286 (100%)
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%)	273 (100%)	290 (100%)	285 (100%)
EORTC QLQ-C30 subscale†				
Functional scales				
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])
Symptom scales				
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†				
Functional scales				
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])
Symptom scales				
Systemic side-effects	271 (8·3 [10·1])	271 (8·1 [10·4])	287 (7·9 [9·5])	286 (8·0 [10·1])
Breast and chest wall 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])

Data are n (mean [SD]) or n (%). CMF=cyclophosphamide, methotrexate, and fluorouracil. EORTC=European Organisation for Research and Treatment of Cancer. HADS=Hospital Anxiety and Depression Scale. QLQ-BR23=Quality of Life Questionnaire 23-item breast module. QLQ-C30=Quality of Life Questionnaire 30-item core module. *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. For functional scales, higher scores indicate good function; for symptom scales and items, higher scores indicate worse symptoms.

Table 2: **Baseline EORTC QLQ-C30, EORTC QLQ-BR23, and HADS scores by treatment group**

	Standard epirubicin		Accelerated epirubicin		p value for end of phase 1 comparison	CMF		Capecitabine		p value for end of phase 2 comparison
	n	Mean (SD)	n	Mean (SD)		n	Mean (SD)	n	Mean (SD)	
HADS scores*										
Anxiety	514	5·6 (4·3)	485	5·2 (4·2)	0·19	467	5·2 (4·2)	492	4·9 (4·0)	0·40
Depression	513	5·0 (3·7)	485	5·3 (4·1)	0·33	467	4·8 (3·8)	492	4·2 (3·7)	0·0048
Total	513	10·6 (7·3)	485	10·6 (7·5)	0·88	467	10·0 (7·2)	492	9·1 (7·0)	0·075
EORTC QLQ-C30 and QLQ-BR23 subscales scores										
Physical functioning†	511	80·3 (18·4)	484	76·8 (20·4)	0·0065	464	76·5 (20·2)	493	79·6 (19·5)	0·0048
Role functioning†	511	65·0 (29·2)	484	56·6 (29·7)	<0·0001	464	60·2 (29·7)	493	64·5 (29·8)	0·013
Fatigue‡	512	44·0 (25·6)	484	50·1 (26·3)	0·0002	464	48·7 (26·6)	493	40·8 (26·6)	<0·0001
Systemic side-effects‡	515	39·1 (19·6)	487	43·8 (19·8)	0·0001	468	35·2 (18·7)	494	29·0 (18·1)	<0·0001
Sexual functioning†	484	16·9 (20·8)	466	16·6 (22·3)	0·36	441	15·5 (20·6)	463	19·6 (23·2)	0·0053
Exploratory analysis										
Emotional functioning†	512	76·0 (22·7)	484	74·3 (23·2)	0·19	465	78·2 (23·2)	493	79·7 (21·1)	0·50
Cognitive functioning†	512	75·0 (23·0)	484	75·2 (22·8)	0·94	465	69·6 (24·9)	493	76·1 (23·1)	<0·0001
Social functioning†	512	67·3 (26·5)	484	61·8 (29·3)	0·0053	465	65·3 (29·1)	493	70·6 (27·2)	0·0043
Nausea and vomiting‡	512	14·6 (19·1)	484	20·5 (20·4)	<0·0001	464	15·3 (21·4)	493	12·2 (18·2)	0·027
Pain‡	512	17·0 (23·4)	484	20·8 (25·4)	0·011	465	16·8 (24·7)	493	18·5 (23·9)	0·074
Dyspnoea‡	511	20·0 (25·2)	484	22·5 (26·7)	0·16	463	27·7 (28·0)	490	18·3 (26·6)	<0·0001
Insomnia‡	510	33·1 (31·2)	484	36·4 (30·4)	0·042	464	41·0 (30·7)	491	32·3 (30·6)	<0·0001
Appetite loss‡	511	22·2 (27·5)	483	30·4 (30·8)	<0·0001	463	22·3 (28·2)	493	19·9 (27·2)	0·16
Constipation‡	512	23·3 (30·1)	484	31·1 (31·5)	<0·0001	464	22·9 (28·8)	491	11·7 (21·6)	<0·0001
Diarrhoea‡	512	11·7 (20·8)	483	13·8 (23·8)	0·31	464	19·3 (28·1)	493	20·4 (28·7)	0·58
Financial difficulties‡	510	24·8 (31·6)	483	22·0 (32·3)	0·046	464	28·0 (33·8)	492	24·9 (32·5)	0·15
Body image†	513	61·9 (29·7)	486	62·6 (29·8)	0·63	461	64·4 (30·7)	490	68·9 (29·0)	0·027
Sexual enjoyment†	174	52·5 (26·9)	157	54·8 (28·0)	0·39	154	54·1 (29·3)	183	55·4 (28·5)	0·64
Future perspective†	513	54·1 (31·2)	484	56·1 (30·7)	0·32	463	53·0 (31·5)	489	54·7 (31·3)	0·39
Breast symptoms‡	515	13·2 (13·9)	487	12·3 (13·8)	0·27	468	11·9 (13·9)	492	12·4 (14·4)	0·55
Arm symptoms‡	514	18·3 (19·6)	486	18·5 (21·9)	0·41	468	13·8 (17·4)	494	14·2 (17·8)	0·91
Hair loss‡	495	38·9 (39·1)	472	43·0 (39·5)	0·099	459	16·8 (32·6)	486	14·3 (30·8)	0·15

p values are from Mann-Whitney non-parametric test. CMF=cyclophosphamide, methotrexate, and fluorouracil. EORTC=European Organisation for Research and Treatment of Cancer. HADS=Hospital Anxiety and Depression Scale. QLQ-BR23=Quality of Life Questionnaire 23-item breast module. QLQ-C30=Quality of Life Questionnaire 30-item core module. *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. †For functional scales higher scores indicates good function; scores range is 0–100. ‡For symptom scales and items higher scores indicate worse symptoms; scores range is 0–100.

Table 3: **Cross-sectional comparisons at the end of each treatment phase**

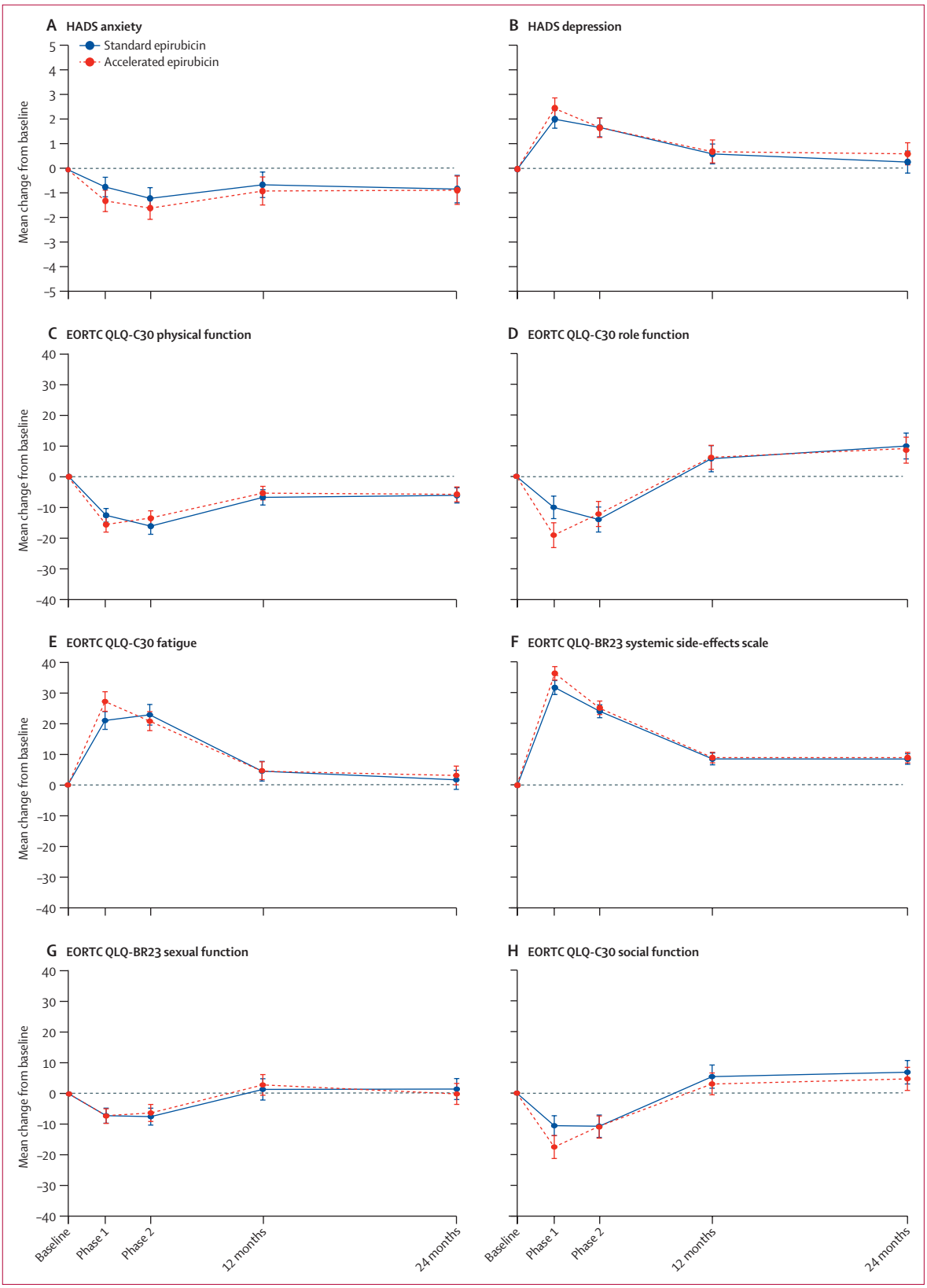
than among postmenopausal patients. Baseline QOL and HADS scores were similar for those who completed the 24-month questionnaire and those who did not.

Participants in the QOL substudy were representative of the TACT2 population (table 1). Data on race and ethnicity were not collected. The baseline questionnaire scores were similar between treatment groups (table 2). Overall, 121 (10·8%) of 1119 participants 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 mean symptom scores.

In the comparison of epirubicin versus accelerated epirubicin, HADS anxiety scores and HADS depression scores were similar between groups at the end of epirubicin or accelerated epirubicin treatment (table 3; appendix p 9). The analysis of the change in HADS scores confirmed a similar pattern to cross-sectional analyses, with no significant differences between epirubicin and accelerated epirubicin (figure 2A–B, appendix pp 14–15). For both treatments, HADS anxiety score improved during the treatment and remained lower than baseline at 24 months, whereas HADS depression score worsened during treatment, followed by improvement at 12 months and 24 months towards baseline levels.

EORTC QLQ-C30 and QLQ-BR23 subscales and items showed significantly worse physical and role function, fatigue, and systemic side-effects for epirubicin versus accelerated epirubicin, but no significant differences in sexual function (table 3).

Prespecified exploratory analysis of the remaining EORTC questionnaire scales and items suggested worse nausea and vomiting, appetite loss, constipation, and social functioning for accelerated epirubicin than with standard epirubicin. Overall, seven of 14 EORTC



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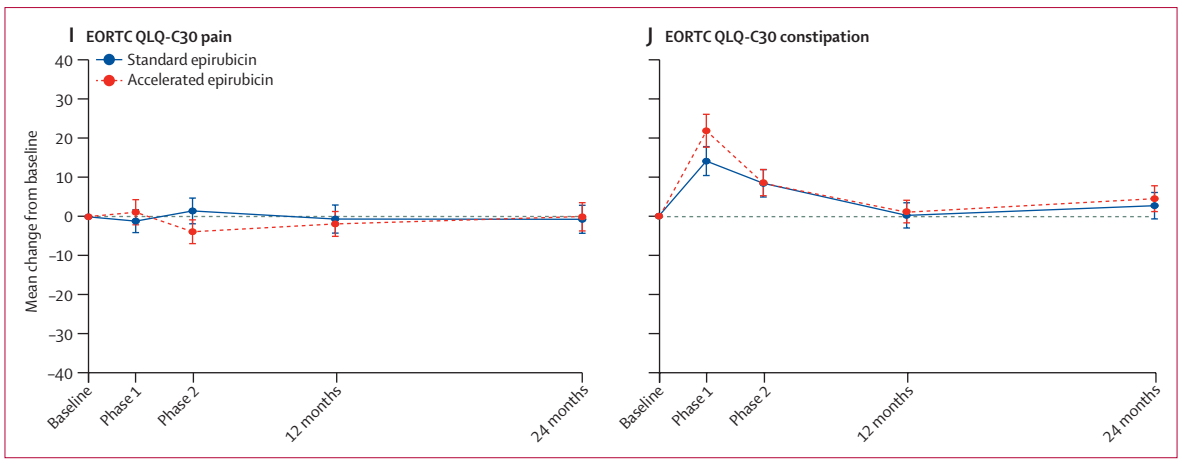


Figure 2: **Mean change in quality of life scores from baseline for standard epirubicin versus accelerated epirubicin**
Whiskers are 99% CIs. For HADS scales and EORTC symptom scales a change greater than 0 means worse scores over time. For EORTC functional scales a change of less than 0 means worse scores over time. EORTC=European Organisation for Research and Treatment of Cancer. HADS=Hospital Anxiety and Depression Scale. QLQ-BR23=Quality of Life Questionnaire 23-item breast module. QLQ-C30=Quality of Life Questionnaire 30-item core module.

QLQ-C30 scores and one of eight EORTC QLQ-BR23 scores were worse in the accelerated epirubicin group compared with standard epirubicin at the end of phase 1 treatment. The negative effect did not persist, with no significant difference between standard epirubicin and accelerated epirubicin at the end of CMF and capecitabine nor at 12 and 24 months (appendix pp 10–13). Analysis of the change in scores showed similar results (figure 2C–J; appendix pp 15–19).

In the responder analysis, 8% to 10% more patients receiving accelerated epirubicin had clinically significant deterioration than those receiving standard epirubicin (appendix p 24). None of these differences remained at the end of CMF or capecitabine treatment, or at 12 or 24 months (appendix pp 24–25).

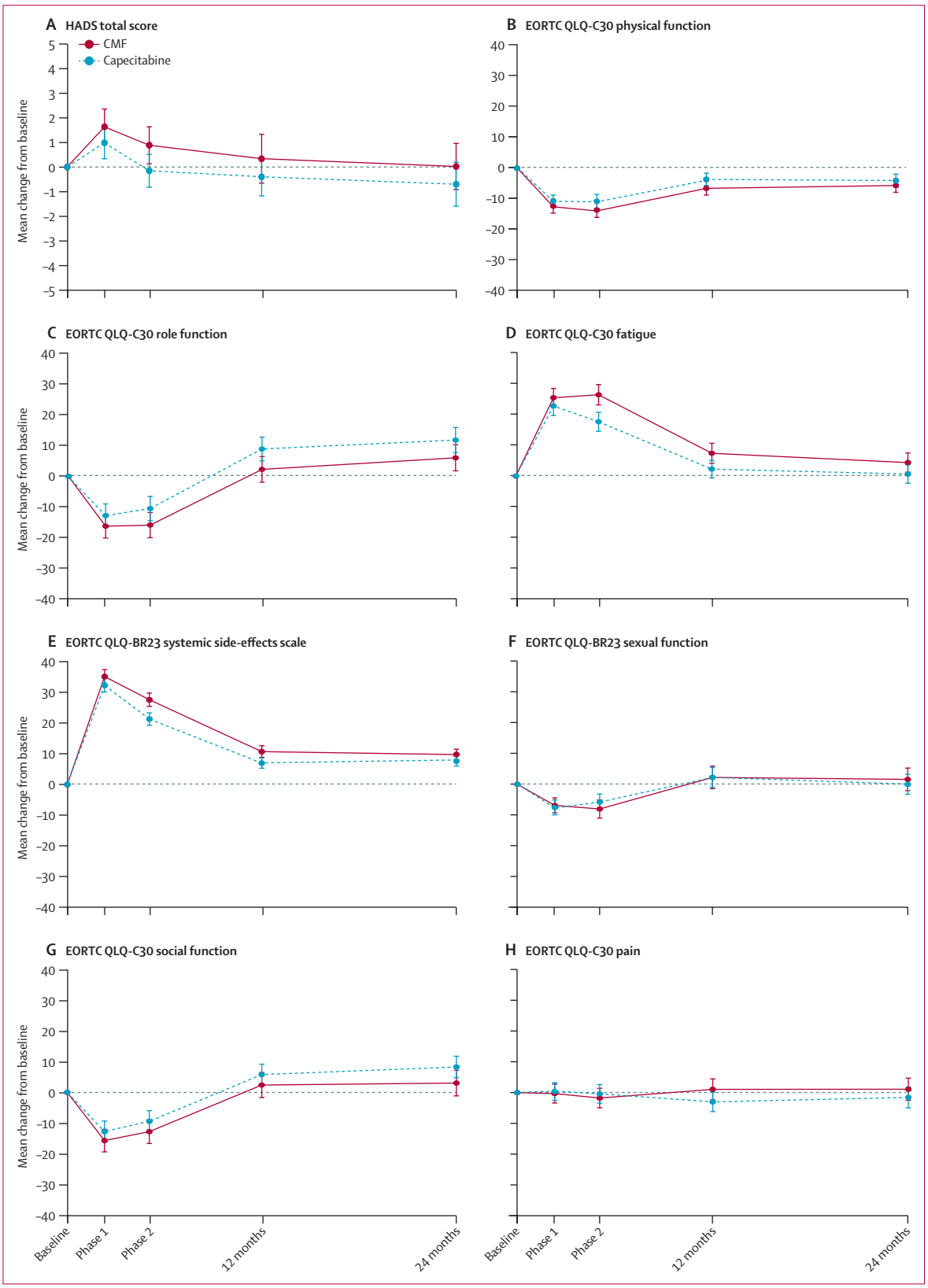
The sensitivity analysis of 577 patients who completed week 6 questionnaires in QL1 showed results consistent with the results of the main analysis, with accelerated epirubicin significantly worse than standard epirubicin for nausea and vomiting, systemic side-effects, global QOL, and role functioning in all analyses (data not shown).

In the comparison of CMF versus capecitabine (table 3; appendix p 9), no between group differences were seen at the end of CMF and capecitabine treatment in the cross-sectional analysis of HADS anxiety score and HADS total score. HADS depression scores were significantly worse in patients who received CMF than patients who received capecitabine (table 3). Change in HADS scores confirmed a similar pattern of no difference, except for HADS total score: at the end of treatment, patients in the CMF group reported worse change scores than patients in the capecitabine group (p=0·0093; appendix p 14), with the difference persistent at 24 months (figure 3A). The worse change score in the CMF group was due to worse HADS depression scores, as HADS anxiety scores improved during the treatment.

Cross-sectional analysis of EORTC questionnaires showed that at the end of CMF or capecitabine treatment, patients on CMF reported significantly worse physical and sexual function, fatigue, and systemic side-effects (table 3). No significant difference was seen for role function.

Prespecified exploratory analysis of the remaining EORTC scales and items suggested worse dyspnoea, insomnia, constipation, and social and cognitive function at the end of treatment with CMF versus capecitabine (table 3). In a post-hoc analysis, we explored if worse dyspnoea was related to anaemia: more patients receiving CMF had grade 1–2 anaemia (70 [18%] of 384) than those on capecitabine (11 [4%] of 290), but there was no association between anaemia severity and dyspnoea scores. Overall, seven of 14 EORTC QLQ-C30 scores and two of eight QLQ-BR23 scores were worse in CMF group at the end of phase 2 treatment. Persistently worse scores in patients receiving CMF than in those receiving capecitabine were observed at 12 months (physical function, role function, fatigue, systemic side-effects, social function, and insomnia) and 24 months (role functioning, fatigue, systemic side-effects, and social function; appendix pp 11–13). Analyses of change in scores showed a similar pattern to the cross-sectional analyses (figure 3B–J; appendix pp 20–23).

The responder analysis of individual patients at the end of CMF and capecitabine showed larger proportions of patients had clinical deterioration in the CMF group than in the capecitabine group in physical function, fatigue, and systemic side-effects but not role or sexual functioning (appendix p 25). Clinically meaningful deteriorations were seen in social function, dyspnoea, insomnia, and 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



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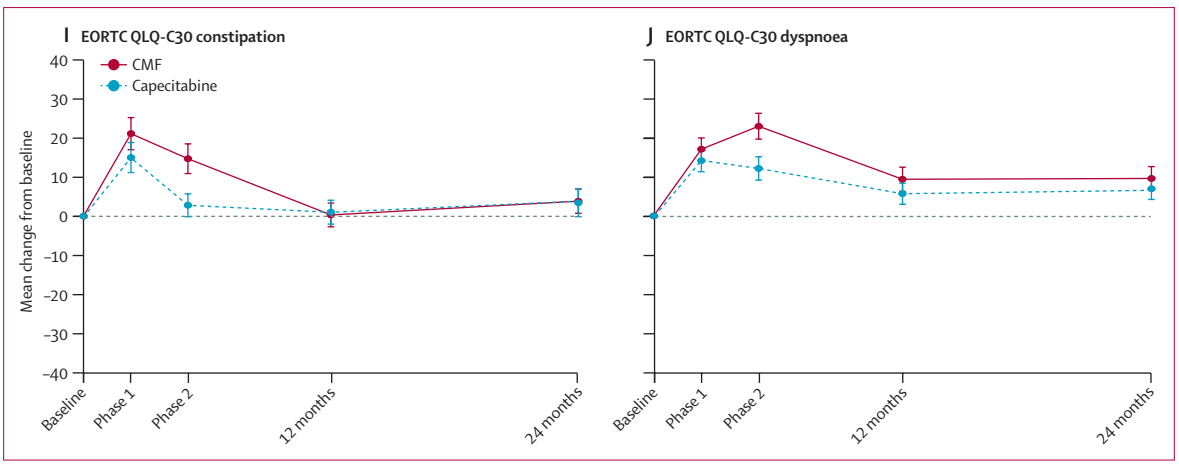

Figure 3: **Mean change in quality of life scores from baseline for CMF versus capecitabine**
Whiskers are 99% CIs. For HADS scales and EORTC symptom scales a change greater than 0 means worse scores over time. For EORTC functional scales a change of less than 0 means worse scores over time. CMF=cyclophosphamide, methotrexate, and fluorouracil. EORTC=European Organisation for Research and Treatment of Cancer. HADS=Hospital Anxiety and Depression Scale. QLQ-BR23=Quality of Life Questionnaire 23-item breast module. QLQ-C30=Quality of Life Questionnaire 30-item core module.

for physical functioning and insomnia. At 24 months, differences were seen for fatigue and role function (appendix p 25).

Longitudinal modelling of HADS scores did not show any significant differences between standard epirubicin and accelerated epirubicin, or between CMF and capecitabine (figure 4; appendix pp 26–32). HADS depression score and HADS total score improved as time from baseline increased. Older age was associated with better HADS anxiety score and HADS total score, but not HADS depression score. Patients who had a mastectomy had higher HADS anxiety scores than those with wide local excision (appendix p 26).

The generalised estimating equation models did not show any significant difference between standard epirubicin and accelerated epirubicin 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 than for capecitabine: nausea and vomiting, dyspnoea, insomnia, appetite loss, constipation, social functioning, cognitive functioning, and body image (appendix pp 26–31). Except pain, and breast and arm symptoms, all EORTC scores improved significantly as time from baseline increased. 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, or breast and arm symptoms. There was no

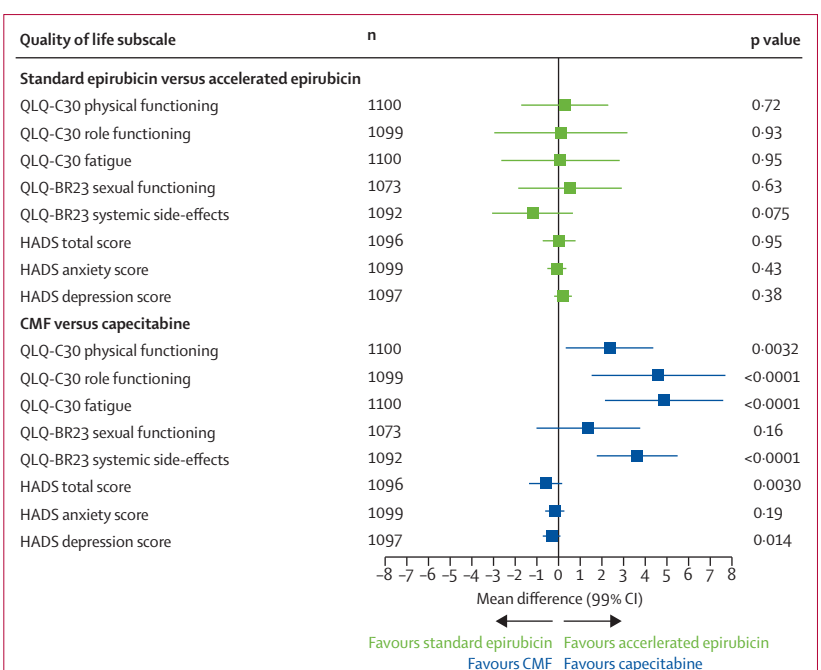

Figure 4: **Forest plots of mean difference in subscale score from generalised estimating equation analysis**
CMF=cyclophosphamide, methotrexate, and fluorouracil. HADS=Hospital Anxiety and Depression Scale. QLQ-BR23=Quality of Life Questionnaire 23-item breast module. QLQ-C30=Quality of Life Questionnaire 30-item core module.

significant difference between the two stages of QOL data collection (QL1 and QL2).

To understand the persistent differences in functioning and symptoms at 24 months, we explored associations between menopausal status at 18 months and the prespecified QOL subscales at 24 months. In post-hoc analyses, changes in scores from baseline to 24 months were compared for three groups of patients:

premenopausal at baseline remaining premenopausal at 18 months (n=154), premenopausal at baseline and postmenopausal at 18 months (n=228), and postmenopausal (n=489). Unadjusted analysis showed that patients whose menopausal status changed reported significantly worse scores on the systemic side-effects subscale (mean change in score 13·2 [SD 12·2]) compared with the postmenopausal group (7·4 [12·2]) or the group remaining premenopausal (7·9 [13·3]; p=0·0008) irrespective of treatment. Responder analysis showed that 64 (50·4%) of the 127 patients in the group whose menopause status changed had clinically meaningful deterioration compared with 137 (28·4%) of 483 in the postmenopausal group and 25 (28·1%) of 89 in the group remaining premenopausal. No differences were seen in physical, role, sexual function, fatigue, pain, or HADS scores (appendix pp 35–36). Regression models adjusting for oestrogen receptor and progesterone receptor status and planned endocrine treatment (four categories: none, tamoxifen, tamoxifen followed by aromatase inhibitor, and aromatase inhibitor) showed similar results (appendix pp 33–44). Patients on any endocrine treatment reported worse physical function compared with those on none.

Discussion

Our results from prespecified secondary QOL analyses confirmed the hypothesis that more intense chemotherapy (ie, accelerated epirubicin and CMF) led to more severe side-effects with greater effect on patient functioning. Patients treated with accelerated epirubicin reported more problems in nine of 23 QOL scales (including global health status/QOL reported previously). Fatigue, treatment side-effects, and physical, role, and social functions were all worse at the end of treatment in the accelerated epirubucin group compared with standard epirubicin. To our knowledge, for the first time we showed that this effect 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 (ten of 23 QOL scales showed worse scores in this group). 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 analysis showed that in the accelerated epirubicin and CMF groups more patients had a clinically meaningful deterioration at the end of treatment compared with standard epirubicin and capecitabine, respectively. Psychological distress measured by HADS was different only in the CMF group where HADS depression score 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 effect on body image or sexual functioning was detected. The emotional impact might 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.

These findings are relevant to present and future patients and clinicians. An individual patient data meta-analysis (which included TACT2 results) confirmed a clinically significant 14% improvement in population outcomes from accelerated anthracycline therapy in patients with early breast cancer, but there were few QOL or toxicity data to help patients make an informed choice regarding cost–benefit balance between accelerated and standard chemotherapy.[8] A pivotal randomised 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] A recent trial and accompanying editorial questioned the value of anthracyclines as part of adjuvant treatment in patients with HER2-positive cancers.[18] Our robust QOL data, in almost 1000 patients (including 21% with HER2-positive cancers), provide an evidence base for informing patients about the type and pattern of this additional toxicity, its effect on functioning and QOL during treatment, and, reassuringly, its resolution after treatment.

Capecitabine is considered by practising oncologists to be a well tolerated chemotherapy with a manageable toxicity profile. Our comparison with CMF confirmed this impression. In a trial of older women (aged ≥65 years), adjuvant chemotherapy with capecitabine showed less severe physical symptoms, better functioning, and better QOL than standard adjuvant chemotherapy (CMF or anthracycline-containing), with the differences resolving by 12 months.[19,20] Our results of the comparison of CMF versus capecitabine in a younger population are consistent with these results, except the 12 months QOL recovery. The differences with the published data might be related to the younger patient population in our trial. We explored if this might be related to the higher amenorrhoea rate in CMF versus capecitabine (data not shown), but the only association

was observed with the systemic side-effects scale. One non-inferiority trial comparing classic 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 the CREATE-X trial[9] it has become standard of care as adjuvant treatment in patients with triple negative breast cancers with poor prognosis and residual disease, following neoadjuvant anthracycline or taxane-containing chemotherapy. The ECOG-ACRIN EA1131 trial[22] supported the use of capecitabine versus platinum in patients with residual triple-negative breast cancer after neoadjuvant chemotherapy. The patient-reported outcomes data in ECOG-ACRIN EA1131 suggested worse side-effects with capecitabine than with 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 substudy is a large, geographically wide UK patient sample. The QOL substudy participating centres were not preselected 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 four 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. The proportion who consented of those who were eligible (85·8%) and compliance with completion of QOL measures (92·0% provided at least one questionnaire after randomisation) is consistent with other similar trials using postal questionnaires over long periods. An overview of 14 clinical trials showed compliance rates per study between 84·7% and 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 might not reflect their experiences. A weakness of the QOL substudy design is the change of the data collection timepoints during the study, dictated by pragmatism. The longitudinal modelling explored the potential effect of the different scheduling and concluded that the results were not different. Another limitation of the QOL substudy is the analysis of available data without imputations or accounting for intercurrent events. This choice was made because the number of intercurrent events was low, without differences between the trial groups, and is unlikely to influence the results.

There is a range of chemotherapy regimens for adjuvant breast cancer treatment. The TACT2 trial showed that if taxanes are not indicated or contraindicated, treatment with epirubicin followed by capecitabine in 3-week cycles is an effective and well tolerated option. This detailed QOL analysis supports the main TACT2 trial conclusion. Although the TACT2 trial did not itself find a significant improvement for accelerated chemotherapy, the subsequent meta-analysis found a reduction in breast cancer recurrences. Adjuvant chemotherapy every 2 weeks is now offered as standard of care in patients with 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 confirm that this additional burden resolves within 1 year of starting therapy. The favourable QOL data on capecitabine support its use as further rescue adjuvant treatment after neoadjuvant 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 and GV oversaw the quality of life substudy. GV, PB-L, HE, DB, AMB, PC, RC, MV, AW, PE, and RS were members of the trial management group. PC and GV did the literature searches. GV, JPM, JSH, and CE did the data analysis, and GV, JPM, JSH, CE, DC, and JMB interpreted the data. GV and JSH accessed and verified the data. GV, PB-L, HE, AMB, PC, RC, MV, AW, and GB recruited patients. AMB and GB were principal investigator recruiters 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. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

GV has received support for the present manuscript from the University of Leeds (payment for time working on manuscript); personal fees from Pfizer, Roche, Eisai, Novartis, Sanofi, and Seagen (none related to the manuscript); and was a member of the European Organisation for Research and Treatment of Cancer board of directors (not related to this manuscript). RC has received personal fees from Sanofi, ACE Oncology, Amgen, and Beigene; has patents planned, issued, or pending with Inbiomotion; personal fees from AstraZeneca; and stock options in Inbiomotion (biomarker in development). MV has received institutional grants from AstraZeneca, Genomic Health, Novartis, Pfizer, and Roche; personal fees from Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Exact Sciences, Gilead, Lilly, Novartis, Pfizer, Roche, and 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) Health Technology Assessment 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); educational grants funding from Roche, Amgen, and Pfizer; and 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, Carnall Farrar, AstraZeneca, Celgene, Eli Lilly, Roche, Novartis, Merck Sharp & Dohme,

PUMA Biotechnology, F Hoffmann-La Roche, Clovis Oncology, Daiichi Sankyo, Eisai, Exact Therapeutics, Genentech, GSK, ICON Clinical Research, Prima BioMED, RTI Health Solutions, Synthon Biopharmaceuticals BV (name changed to Byondis in April, 2020), Succinct Medical Communications, Seagen, Sanofi, Sapience Therapeutics, Bexon/Zymeworks Biopharmaceuticals, NexGen, and IQVIA; institutional grants from Cancer Research UK, Health Technology Assessment, Breast International Group, Breast Cancer Institute, and European Cancer Organisation. All other authors declare no competing interests.

Data sharing

De-identified individual participant data, together with a data dictionary defining each field in the set, will be made available to other researchers on request. Formal requests for data sharing are considered in line with Institute of Cancer Research Clinical Trials and Statistics Unit procedures, with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement, which describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the trial management group in terms of scientific merit and ethical considerations, including patients' consent.

Acknowledgments

We thank the patients, their relatives and treating clinicians, and the hospitals who participated in this study. We acknowledge especially the Cancer Clinical Trials Unit, Edinburgh, UK for coordinating the collection of the quality of life 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 National Health Service (NHS) research and development 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 cosponsoring organisations, The Institute of Cancer Research and NHS Lothian. Roche supplied free capecitabine and Amgen provided subsidised pegfilgrastim for trial use.

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