Adjuvant docetaxel, doxorubicin, and cyclophosphamide in node-positive breast cancer: 10-year follow-up of the phase 3 randomised BCIRG 001 trial

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Background We compared standard adjuvant anthracycline chemotherapy with anthracycline–taxane combination chemotherapy in women with operable node-positive breast cancer. Here we report the final, 10-year follow-up analysis of disease-free survival, overall survival, and long-term safety.

Methods BCIRG 001 was an open label, phase 3, multicentre trial in which 1491 patients aged 18–70 years with node-positive, early breast cancer and a Karnofsky score of 80% or more were randomly assigned to adjuvant treatment with docetaxel, doxorubicin, and cyclophosphamide (TAC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC) every 3 weeks for six cycles. Randomisation was stratified according to institution and number of involved axillary lymph nodes per patient (one to three *vs* four or more). Disease-free survival was the primary endpoint and was defined as the interval between randomisation and breast cancer relapse, second primary cancer, or death, whichever occurred first. Efficacy analyses were based on the intention-to-treat principle. BCIRG 001 is registered with ClinicalTrials.gov, number NCT00688740.

Findings Enrolement took place between June 11, 1997 and June 3, 1999; 745 patients were assigned to receive TAC and 746 patients were assigned to receive FAC. After a median follow-up of 124 months (IQR 90–126), disease-free survival was 62% (95% CI 58–65) for patients in the TAC group and 55% (51–59) for patients in the FAC group (hazard ratio [HR] 0·80, 95% CI 0·68–0·93; log-rank p=0·0043). 10-year overall survival was 76% (95% CI 72–79) for patients in the TAC group and 69% (65–72) for patients in the FAC group (HR 0·74, 0·61–0·90; log-rank p=0·0020). TAC improved disease-free survival relative to FAC irrespective of nodal, hormone receptor, and HER2 status, although not all differences were significant in these subgroup analyses. Grade 3–4 heart failure occurred in 26 (3%) patients in the TAC group and 17 (2%) patients in the FAC group, and caused death in two patients in the TAC group and four patients in the FAC group. A substantial decrease in left ventricular ejection fraction (defined as a relative decrease from baseline of 20% or more) was seen in 58 (17%) patients who received TAC and 41 (15%) patients who received FAC. Six patients who received TAC developed leukaemia or myelodysplasia, as did three patients who received FAC.

Interpretation Our results provide evidence that the initial therapeutic outcomes seen at the 5-year follow-up with a docetaxel-containing adjuvant regimen are maintained at 10 years. However, a substantial percentage of patients had a decrease in left ventricular ejection fraction, probably caused by anthracycline therapy, which warrants further investigation.

Funding Sanofi.

Introduction

Addition of a taxane to adjuvant anthracycline-based regimens improves relapse-free survival and overall survival in patients with early breast cancer.[1] The Breast Cancer International Research Group (BCIRG) 001 study showed that a regimen that incorporates the taxane docetaxel reduces the risk of relapse (HR 0·72, 95% CI 0·59–0·88; p=0·001) and death (HR 0·70, 95% CI 0·53–0·91; p=0·008) compared with a standard anthracycline-based regimen in patients with node-positive, early breast cancer, as we previously reported[2] after 55 months of follow-up. However, the long-term risks and benefits of adjuvant chemotherapy remain poorly understood, since many studies have not reported long-term outcomes,[3] some have had substantial loss to follow-up, and most did not monitor subclinical toxic effects such as left ventricular dysfunction. Furthermore, an emerging understanding of the distinct molecular subtypes of breast cancer[4] now allows for assessment of differential benefits from chemotherapy, endocrine therapy, and biologically targeted drugs.

Here we report the long-term efficacy and safety results from this large, mature, randomised study of adjuvant taxane chemotherapy, on the basis of an intention-to-treat analysis of all 1491 participants.

Methods

Patients and study design

As previously reported,[2] women eligible for this phase 3, multicentre, open label, randomised trial were aged between 18 and 70 years, had a score on the Karnofsky performance scale of 80% or more, and had undergone primary surgery (ie, mastectomy or lumpectomy) for unilateral, operable breast cancer in which clear margins were obtained, and with axillary lymph node dissection that returned at least one positive node on histological examination (from a minimum of six nodes). A complete staging investigation—including bilateral mammography; chest radiography; abdominal ultrasonography, CT, or both; and bone scanning—and an assessment of the left ventricular ejection fraction with the use of multiple gated acquisition scanning or echocardiography were mandatory at baseline (ie, within 3 months of registration). Criteria for exclusion included advanced disease (ie, T4, N2 or N3, or M1), a history of other cancers, motor or sensory neuropathy of grade 2 or higher according to the US National Cancer Institute (NCI) common toxicity criteria,[5] pregnancy, lactation, and any serious illness or medical disorder other than breast cancer.

The ethics committees of all participating institutions approved the study. All patients provided written informed consent. The trial was done in accordance with the International Conference on Harmonisation Good Clinical Practice Guidelines, including verification of source data.

Randomisation and masking

Randomisation was stratified according to institution and number of involved axillary lymph nodes per patient (one to three *vs* four or more). Computer-generated randomisation lists were used for each stratum (centre and number of nodes) and were balanced with a block size of four. Random assignment was done with an interactive voice response system and treatment allocation was immediately communicated to the investigator. Patients and treating physicians could not be masked to allocation because of the nature of the interventions, and investigators were not masked since the outcomes (relapse, death) were objective.

Procedures

Patients were randomly assigned to receive either adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) or fluorouracil, doxorubicin, and cyclophosphamide (FAC). On day 1 of each of six 21-day cycles, patients were given either 50 mg of doxorubicin per m² of body-surface area in an intravenous infusion for 15 min, followed by 500 mg of cyclophosphamide per m² given intravenously for 1–5 min and then, after an interval of 1 h, 75 mg of docetaxel per m² in an intravenous infusion for 1 h (TAC group) or 50 mg of doxorubicin per m² followed by 500 mg of fluorouracil per m², each as an intravenous infusion for 15 min, and then 500 mg of cyclophosphamide per m² in an intravenous infusion for 1–5 min (FAC group). Patients assigned TAC were given dexamethasone premedication (8 mg orally every 12 h, six times beginning the day before start of treatment) to prevent docetaxel-related hypersensitivity and fluid retention, and a prophylactic antibiotic (500 mg of ciproloxacin twice daily on days 5–14 of each cycle). Primary prophylaxis with granulocyte colony-stimulating factor (G-CSF) was not permitted. However, in patients who had an episode of febrile neutropenia or infection, G-CSF was mandatory in subsequent cycles. Dose modifications were planned according to standard toxicity criteria. Discontinuation of treatment was required for patients in whom there were non-haematological grade 4 toxic effects according to the NCI common toxicity criteria,[5] grade 3 toxic effects despite a dose reduction, or clinically significant cardiac events.

On completion of chemotherapy, tamoxifen (20 mg daily for 5 years) was given to patients with hormone receptor-positive tumours. Radiotherapy was mandatory after breast-conserving surgery and was given after mastectomy according to each institution's guidelines.

Patients were followed in clinic every 3 months for the first 2 years, every 6 months up to year 5, and annually from years 5 to 10. Mammography was done every year until year 10, and chest radiography was done every year until year 5. After baseline assessment, left ventricular ejection fraction was only assessed during the first 5 years of follow-up in patients with symptoms of clinical

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See **Online** for appendix

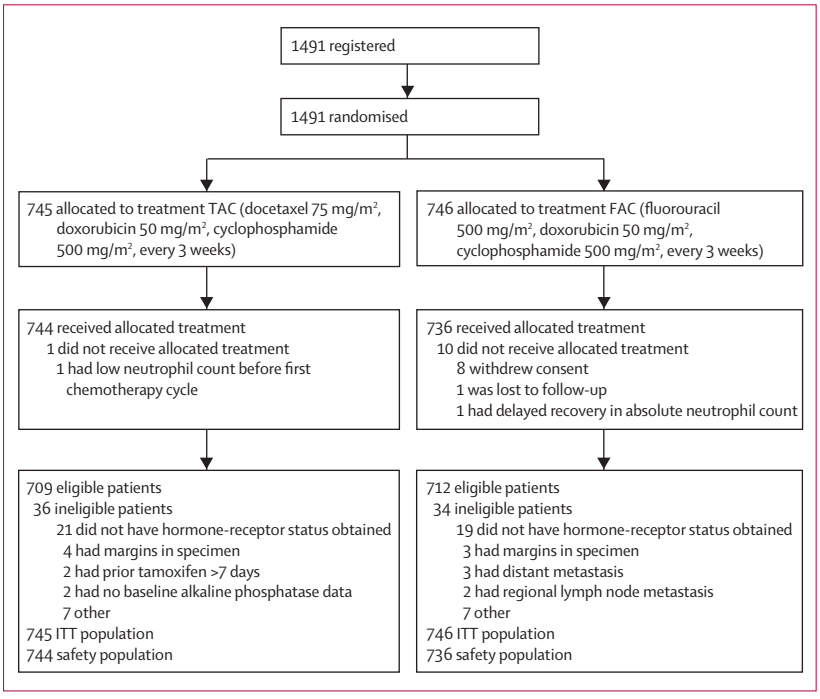

Figure 1: **Trial profile**
ITT=intention-to-treat.

heart failure. However, after a protocol amendment, left ventricular ejection fraction for each patient was measured annually from years 5 to 10 to explore long-term cardiac effects. Adverse events were coded as per NCI common toxicity criteria.[5] Acute side-effects associated with adjuvant chemotherapy and specific toxic effects linked with individual agents were monitored for all patients and previously reported.[2] The focus of this 10-year final report is the follow-up period (ie, more than 30 days after the last administration of chemotherapy).

Central pathology review was done for 1372 (92%) patients, during which the HER2 (ERBB2) status of all tumours was confirmed by use of fluorescence in-situ hybridisation (PathVysion, Abbott Molecular, Abbott Park, IL, USA), and central assessments of oestrogen receptor status, progesterone receptor status, and Ki67 proliferation indices (clone Mib1 antibody [Dako, Glostrup, Denmark]; cut-point 13%) were done by immunohistochemical tests. Analyses by molecular subgroup were not prespecified in the original protocol. Immunohistochemically defined subsets of patients were examined to test the prognostic and predictive usefulness of these subsets in a clinical trial setting, as previously reported.[6]

	TAC group (N=745)	FAC group (N=746)
Age (years)	49 (42–55)	49 (43–56)
Karnofsky performance score	100% (100–100)	100% (100–100)
Premenopausal	421 (57%)	409 (55%)
Mastectomy	445 (60%)	438 (59%)
Radiotherapy	512/744 (69%)	529/736 (72%)
Tamoxifen	509/744 (68%)	507/736 (69%)
Mean left ventricular ejection fraction in mL (SD)	64·2 (56·1–72·3)	64·4 (56·5–72·3)
Primary tumour size (cm)		
≤2	295 (40%)	320 (43%)
>2 to 5	393 (53%)	383 (51%)
>5	57 (8%)	43 (6%)
Number of involved axillary nodes		
1–3	463 (62%)	460 (62%)
4 or more	282 (38%)	286 (38%)
Hormone-receptor positive*	567 (76%)	565 (76%)
HER2 status*†		
Negative	513 (69%)	492 (66%)
Positive	155 (21%)	164 (22%)
Unknown	77 (10%)	90 (12%)
Intrinsic subtype*		
Undefined	77 (10%)	88 (12%)
HER2 with negative hormone receptors	56 (8%)	57 (8%)
Luminal A	104 (14%)	107 (14%)
Luminal B	409 (14%)	401 (54%)
Triple negative	99 (13%)	93 (12%)

Unless otherwise indicated, data are median (IQR) or n (%). Percentages are of the intention-to-treat population apart from for radiotherapy and tamoxifen, which are given as percentages of the safety population because these were given after study treatment. Some data differ from those published in reference 2 because of data cleaning. TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. *Reviewed centrally. †HER2 status was determined by fluorescence in-situ hybridisation (FISH), or by immunohistochemistry in the few cases in which FISH was not available.

Table 1: **Baseline patient and tumour characteristics**

	TAC group (N=745)	FAC group (N=746)
Lost to follow-up	43 (6%)	39 (5%)
First event		
Local relapse	32 (4%)	36 (5%)
Regional relapse	9 (1%)	14 (5%)
Distant relapse	174 (23%)	214 (29%)
Second primary cancer	56 (8%)	53 (7%)
Death, no evidence of disease	15 (2%)	16 (2%)
Undefined event	1 (<1%)	0
Total events	287 (39%)	333 (45%)

Events are those included in the analysis of disease-free survival. TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide.

Table 2: **Events by intention to treat at 10-year follow-up**

Statistical analysis

This final analysis was triggered after a median of 10 years' follow-up in surviving patients, with the data cutoff date of March 11, 2010. Efficacy analyses were done according to the intention-to-treat principle. Safety analyses were done in the safety population (which consisted of all patients who received at least one dose of their assigned treatment), apart from analyses of left ventricular ejection fraction, which were done for all evaluable patients (ie, those patients with a left ventricular ejection fraction assessment at baseline and at least one repeat assessment during the total study period, including follow-up). For the assessments of left ventricular ejection fraction, patients were deemed non-evaluable if a primary event occurred before the repeat assessment or if a non-protocol anticancer therapy had been given.

The trial was designed to have an overall power of 97% to detect a 27% reduction in risk of relapse in patients treated with TAC as compared with those treated with FAC, irrespective of nodal status. Additionally, the study was designed to have 90% power to detect a 33% reduction in risk of death. The sample size of 1491 patients also allowed the detection, with 90% power, of a 27% reduction in risk of relapse in favour of treatment with TAC in patients who had one to three positive lymph nodes. For the subgroup of patients with four or more positive nodes, the sample size provided 80% power to detect a 29% reduction in risk of relapse in favour of treatment with TAC.

The primary endpoint was disease-free survival, defined as the time from randomisation to the date of a clinical relapse, a second cancer (excluding skin cancer other than melanoma and carcinoma in situ of the breast or cervix), or death, whichever occurred first; disease-free survival in the two treatment groups was assessed by the log-rank test, stratified according to number of involved axillary nodes (one to three *vs* four or more).

Secondary endpoints included overall survival (ie, the time from randomisation until death from any cause), toxic effects, and quality of life.[7] We did unadjusted analyses and analyses according to the Cox proportional hazards model (adjusted for age, tumour size, nodal status, hormone-receptor status, and HER2 status) to estimate hazard ratios (HRs) and 95% CI for disease-free survival and overall survival. We used Kaplan-Meier analysis to calculate probability estimates of disease-free survival and overall survival. All p values reported are two-sided and all analyses were done with SAS version 9.0 (SAS Institute, Cary, NC, USA). Demographic and safety analyses were done by the sponsor's statistician. Interim efficacy analyses were done by a statistician from an independent data monitoring committee, whereas the final efficacy analysis was done by the sponsor's statistician. Results of analyses were presented to the independent data and safety monitoring committee.

The BCIRG 001 study is registered at ClinicalTrials.gov, number NCT00688740. The treatment protocol is available from the Translational Research in Oncology website.

Role of the funding source

Study design, conduct, and analyses were agreed on by the sponsor and the study coordinators. Data collection was done by BCIRG 001/TRIO investigators. The trial steering committee included representatives of the sponsor. A reviewer at the study sponsor assessed the report but did not participate in writing it. The final content of the report was decided entirely by the investigators. The raw data were accessible by MM, JRM, M-AL, VW, MR, and VH. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Between June 11, 1997, and June 3, 1999, 1491 women from 20 countries in Europe, North and South America, Africa, and the Middle East were enrolled in the study (figure 1). Specific demographic, clinical, and molecular phenotypic characteristics of patients were well-balanced between the group assigned to receive the TAC regimen and the group assigned to receive the FAC regimen (table 1). Compliance with the study protocol was high, with fewer than 6% of participants (43 from the TAC group and 39 from the FAC group) lost to 10-year follow-up.

At the time this analysis was triggered, median follow-up was 124 months (IQR 103–126) for the TAC group and 123 (78–126) months for the FAC group. 620 primary events had occurred by data cutoff (table 2). 10-year disease-free survival was 62% (95% CI 58–65) for the TAC group, compared with 55% (51–59) for the FAC group (HR 0·80, 95% CI 0·68–0·93; log-rank p=0·0043; figure 2A). 429 deaths had occurred by data cutoff: 188 in the TAC group and 241 in the FAC group. 10-year overall survival was 76% (72–79) in the TAC group compared with 69% (65–72) in the FAC group (HR 0·74, 95% CI 0·61–0·90; log-rank p=0·0020; figure 2B). Forest plot analyses for disease-free survival and overall survival by patient subgroups (including number of positive lymph nodes, hormone receptor status, HER2 status, and menopausal status) show benefit from TAC compared with FAC across these subgroups, although not all differences were significant (figure 3). However, an exploratory analysis of the effect of intrinsic molecular breast cancer subtype[6] suggests that the luminal A

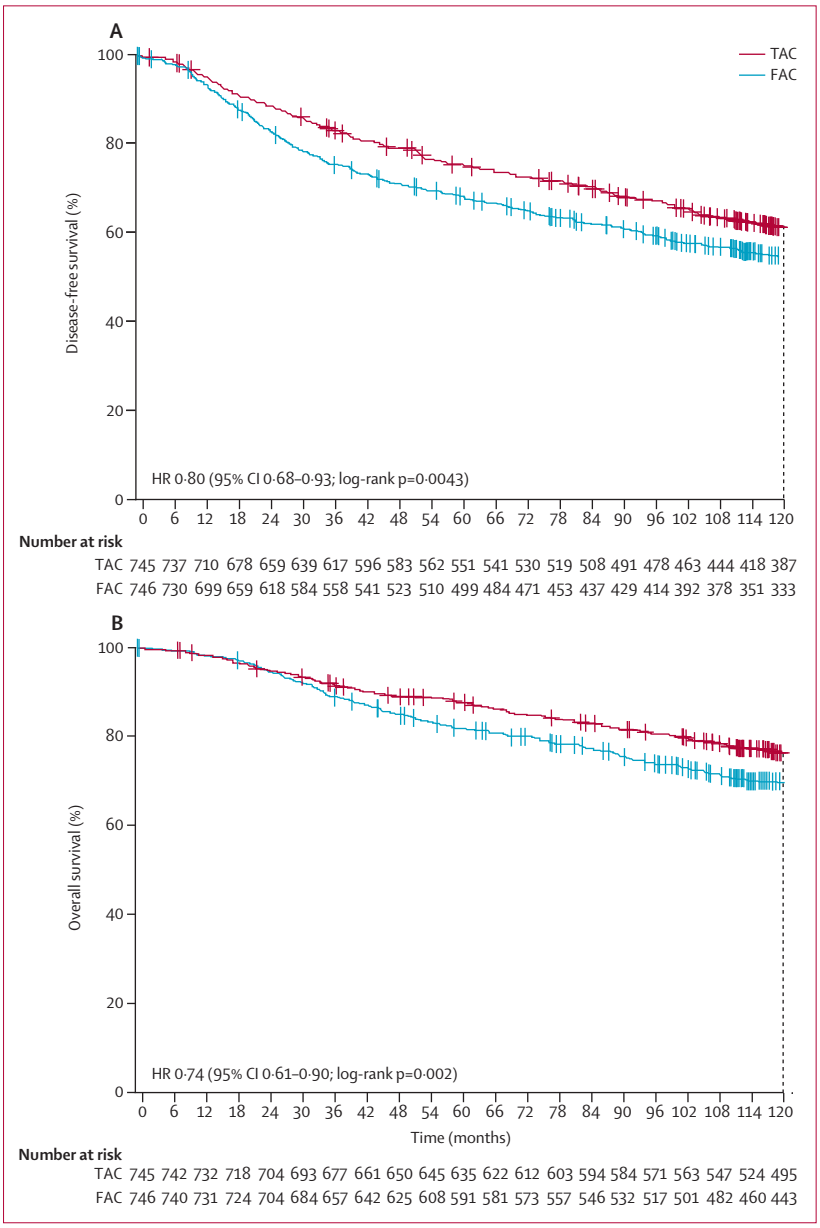

Figure 2: **Disease-free survival (A) and overall survival (B) for all patients, by treatment group**
TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. HR=hazard ratio.

For the **Translational Research in Oncology website** see http://www.trioncology.org/html/docs/BCIRG%20001%20protocol.pdf

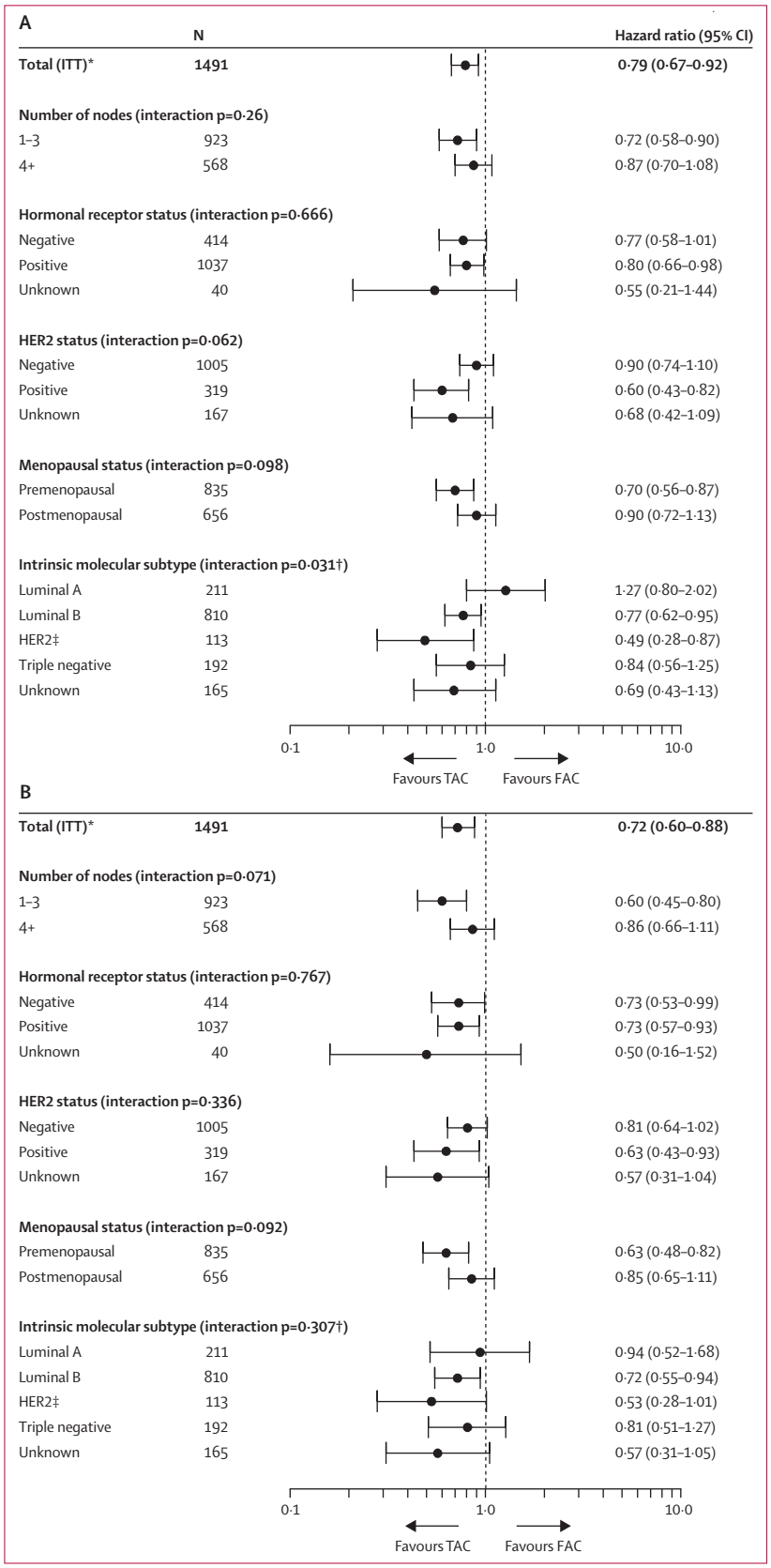

Figure 3: **Subgroup analyses of disease-free survival (A) and overall survival (B)** Premenopausal patients included those whose menopausal status was unknown but who were younger than 50 years; postmenopausal patients included those whose menopausal status was unknown but who were aged 50 years or older. The difference in disease-free survival between luminal A and luminal B molecular subtypes is significant (log-rank p=0·021). TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. ITT=intention to treat. *The hazard ratios and 95% CIs presented here differ from the analyses in figure 2 because of adjustment based on number of lymph nodes as reported on case report forms, rather than number of lymph nodes reported at randomisation. †Interaction test for intrinsic molecular subtypes compares luminal A with non-luminal A subtypes. ‡HER2 intrinsic subtype is HER2-positive with negative hormone receptors.

population, a group of patients whose tumours were low proliferation rate, hormone receptor-positive, and did not show amplification or overexpression of HER2, did not derive benefit from adjuvant taxane therapy (figure 3). Conversely, the luminal B, HER2-positive with negative hormone receptors, and triple negative populations might derive disease-free survival benefit from TAC chemotherapy compared with the FAC regimen, although not all differences were significant (figure 3).

Serious adverse events, as per the US Food and Drug Administration definition of an undesirable experience that is life-threatening, requires hospitalisation, or leads to death, disability, or permanent damage, were largely confined to the period of chemotherapy, and occurred at reduced rates during follow-up (TAC group: 53 [7%] patients during follow-up, compared with 267 [36%] during treatment phase; FAC group: 33 [4%] during follow-up, compared with 67 (9%) during treatment phase). The most common adverse events that persisted into the follow-up period were asthenia (236 [32%] patients in the TAC group *vs* 180 [24%] in the FAC group; χ^2 p=0·0019; Fisher's exact p=0·0022) and amenorrhoea in premenopausal patients (198 [47%] of 420 premenopausal women in the TAC group *vs* 119 [30%] of 403 in the FAC group; χ^2 p<0·0001; Fisher's exact p<0·0001). The frequencies of cardiac and haematological adverse events that started or worsened during follow-up were similar between the two treatment groups, but peripheral sensory neuropathy was more common in patients given taxane therapy (28 [4%] patients in the TAC group *vs* 5 [1%] in the FAC group (χ^2 and Fisher's exact p<0·0001). Haematological malignancies were reported in six (1%) patients treated with TAC and three (<1%) patients treated with FAC (p=0·51 [Fisher's exact test]; table 3).

At study entry, cardiac risk factors were well balanced between the treatment groups (data not shown). Frequency of congestive heart failure (defined as NCI cardiac function grade 3–4) was similar in both groups (table 4). Although most cases were grade 3, congestive heart failure was fatal in two TAC-treated patients and four FAC-treated patients (p=0·450 [Fisher's exact test]; table 4). The timing of onset of congestive heart failure is shown in figure 4. The number of evaluable patients with substantial decreases in left ventricular ejection fraction

after chemotherapy (relative decrease from baseline of 20% or more) was similar between the treatment groups (table 5). The percentage of patients with congestive heart failure who did not have baseline risk factors (eg, age, diabetes, obesity, hypercholesterolemia, hyperlipidaemia, left-side radiation therapy, or hypertension) was similar in both treatment groups (4 [15·4%] patients in the TAC group *vs* 3 [17·6%] in the FAC group).

Discussion

This 10-year analysis of the BCIRG 001 study shows that adjuvant TAC for treatment of women with node-positive, early breast cancer provides long-term disease-free survival and overall survival benefits compared with FAC, with similar long-term toxic effects (panel). However, anthracycline-induced cardiotoxicity is a serious and under-recognised complication of adjuvant anthracycline-based chemotherapy regimens that warrants further attention.

The risk-to-benefit ratio of adjuvant breast cancer chemotherapy is highly sensitive to the interplay of efficacy and the late toxic effects in long-term survivors, many of whom will have been cured by surgery alone. Although adjuvant systemic therapy for early stage breast cancer has clearly improved survival, the long-term outcomes after modern adjuvant chemotherapy are largely unknown because of trial designs that do not mandate extended observation, loss of study participants from follow-up, and the expense of long-term follow-up in trials that assess drugs that for the most part are now available off-patent. These factors seem to introduce a systematic bias into the assessment of chemotherapy efficacy-to-toxic effects ratios, since the hazard ratios for relapse-free effects reported in clinical trials are often most favourable with short-term follow-up, and are attenuated with additional follow-up either because of the loss of therapeutic efficacy, the effect of competing causes of mortality, and the late life-altering and life-threatening complications of cardiac failure and myelodysplasia or leukaemia.

On the basis of the Early Breast Cancer Trialists' Collaborative Group meta-analysis[8] that showed improved efficacy of anthracycline compared with non-anthracycline chemotherapy regimens, most modern adjuvant therapy incorporates anthracyclines. Because of the preclinical and clinical evidence of incomplete cross-resistance between anthracycline and taxane chemotherapy regimens, BCIRG 001 was designed to assess the concurrent administration of docetaxel with anthracycline-based chemotherapy.[2] The results of this 10-year follow-up analysis accords with our previous results, and show that adjuvant TAC provides a long-term disease-free survival and overall survival benefit for women with node-positive, early breast cancer, in comparison with adjuvant FAC. The absolute survival benefit seen at 5 years of follow-up (6%) has been maintained at this 10-year update (7%). All subgroups of patients seem to derive benefit from adjuvant TAC, with the apparent exception of the biologically defined group of patients with luminal A disease (figure 3A).[6] With the exception of the nodal subgroup analysis, the subgroup analyses shown in figure 3 are exploratory and were not specifically powered to detect differences between the two treatment groups.

	TAC group (N=744)	FAC group (N=736)	p value*
Acute myeloid leukaemia	4 (<1%)	1 (<1%)	0·374
Chronic lymphocytic leukaemia	0	1 (<1%)	0·450
Myelodysplasia	2 (<1%)	1 (<1%)	1·000

TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. *Fisher's exact test.

Table 3: **Haematological malignancies (safety population)**

	TAC group (N=744)	FAC group (N=736)	p value*	p value†
Congestive heart failure (cardiac function grade 3–4)	26 (3%)	17 (2%)	0·175	0·215
Grade 3 (mild, responsive to therapy)	21 (3%)	14 (2%)	0·244	0·305
Grade 4 (severe, refractory)	5 (1<%)	3 (<1%)	NA	0·726
Serious cardiac adverse event	23 (3%)	16 (2%)	0·270	0·330
Death due to congestive heart failure	2 (<1%)	4 (<1%)	NA	0·450

TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. *χ^2 test. †Fisher's exact test.

Table 4: **Cardiac adverse events (safety population)**

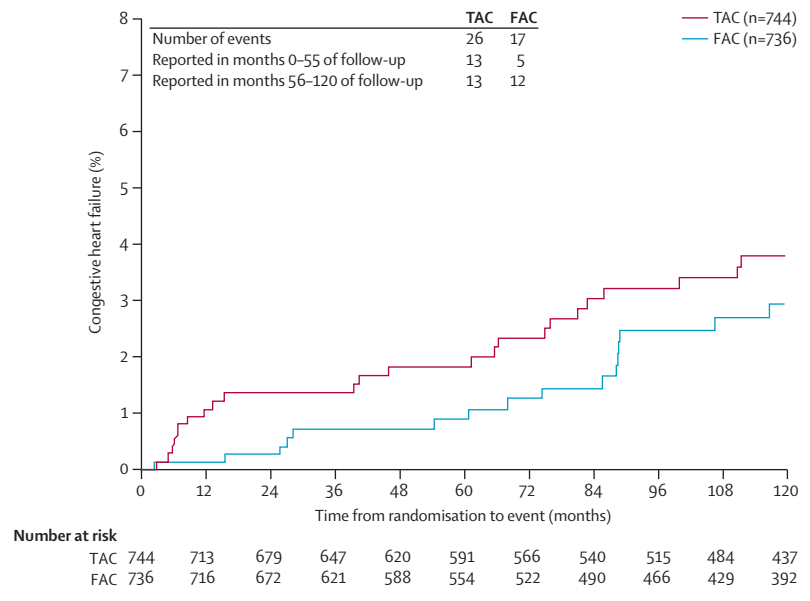

Figure 4: **Cumulative frequency of congestive heart failure**
Frequency of congestive heart failure increased in both groups throughout the study, but did not significantly differ between the two groups, either in absolute terms or in time-dependent analyses. TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide.

	TAC group (N=348)	FAC group (N=269)	p value*	p value†
LVEF decrease >20% (% of evaluable patients)	58 (17%)	41 (15%)	0·632	0·660
LVEF decrease below lower normal limit‡ (% of evaluable patients)	41 (12%)	27 (10%)	0·492	0·520

TAC=docetaxel, doxorubicin, and cyclophosphamide. FAC=fluorouracil, doxorubicin, and cyclophosphamide. LVEF=left ventricular ejection fraction. *χ^2 test. †Fisher's exact test. ‡Lower limit of normal was defined by each investigator's individual institution (or 50% if institutional limit was not reported).

Table 5: **Changes in left ventricular ejection fraction (evaluable population)**

***Panel:* Research in context**

Systematic review

When this analysis was planned, we searched PubMed for all available evidence from phase 3 trials of adjuvant therapy for breast cancer, using the search terms "breast cancer", "adjuvant", "adjuvant treatment", "adjuvant chemotherapy", "adjuvant hormonal therapy", "phase III study". The same approach was also used in the preparation of this report.

Interpretation

Our findings show that the improved efficacy of adjuvant docetaxel, doxorubicin, and cyclophosphamide (TAC) compared with fluorouracil, doxorubicin, and cyclophosphamide (FAC) for women with node-positive, early breast cancer reported at 5 years persists, for both disease-free survival and overall survival, at 10 years. However, careful cardiac assessment identified a substantial percentage of patients with decreases in left ventricular ejection fraction, probably caused by anthracycline therapy.

Our efficacy results are consistent with other studies.[1,9] However, the BCIRG 001 study is the first modern, three-drug regimen for which 10-year outcomes have been reported, and adds to our understanding of the long-term safety of adjuvant anthracycline and taxane use. As expected, we saw that the taxane-specific toxic effects of persistent neuropathy were increased when compared with the non-taxane control arm. Anthracycline-associated long-term toxic effects include significant increases in congestive heart failure,[10,11] myelodysplasia, and acute leukaemia.[12,13] Consistent with the known effects of anthracyclines and cyclophosphamide, haematological malignancies were reported in six patients treated with TAC and three patients treated with FAC. However, our results suggest that the long-term cardiovascular toxic effects of standard-dose anthracycline chemotherapy have been underappreciated and need to be revisited.

Within BCIRG 001, cardiovascular toxic effects were carefully monitored and protocol-specified investigations included confirmation of normal resting cardiac baseline function before admission into the study. Left ventricular ejection fraction does not fall with time in the absence of a cardiac insult.[14] Despite the fairly young age of this population (median age 49 years), and a standard dose and schedule of anthracycline administration, about 16% of patients had at least a 20% relative reduction in left ventricular ejection fraction from their pre-anthracycline baseline. Such a drop reflects a substantial loss of cardiac reserve that increases susceptibility to overt heart failure with the comorbidities that accompany ageing, including hypertension, diabetes, and cardiac ischaemia.[15] Furthermore, the time course of the development of clinical congestive heart failure is not reassuring. Figure 4, which shows the cumulative frequency of congestive heart failure, shows no suggestion of a plateau in rates up to 10 years, which suggests that the long-term survivors of early stage breast cancer have continued and potentially indefinite long-term risks of congestive heart failure. In our study, congestive heart failure was reported in 26 (3%) patients treated with TAC and 17 (2%) patients treated with FAC. Most cases were grade 3, but congestive heart failure was fatal in two patients treated with TAC and four patients treated with FAC. Roughly 16% of the patients who developed congestive heart failure had no cardiac risk factors apart from anthracycline exposure.

Our results contrast with those reported in a global individual patient meta-analysis,16 in which the rate of heart disease after adjuvant anthracycline therapy was only 0·08% per year, a non-significant increase of only 0·02 percentage points per year compared with non-anthracycline chemotherapy. Although no other adjuvant anthracycline study has systematically gathered and reported 10-year asymptomatic and clinical cardiac outcomes, investigators of the FASG 05 study reported[17] on a subset of 150 patients at a median of 8 years after adjuvant anthracycline therapy; 2 (2·3%) patients who received 600 mg/m² of adjuvant epirubicin had symptomatic congestive heart failure, and 18 (21·1%) had asymptomatic left ventricular dysfunction. Our results are also consistent with epidemiologic data from the Surveillance, Epidemiology, and End Results database in which women older than 65 years who received adjuvant anthracycline-based chemotherapy for breast cancer had substantially higher risks of congestive heart failure than did those who received non-anthracycline adjuvant chemotherapy agents, and the absolute differences in frequency of congestive heart failure increased through more than 10 years of follow-up.[11] These findings are consistent with our understanding that anthracyclines cause irreversible damage to myocardial cells through generation of free radicals and myocardial apoptosis.[18] Although the injury is acute, clinical signs and symptoms can take months or years to

manifest,[19] which suggests that cardiac reserve continues to decrease in anthracycline-treated breast cancer survivors, and that the long-term risk-to-benefit ratio of anthracyclines in early breast cancer should be further studied.

The BCIRG 001 study has important strengths that increase our confidence in these long-term results. The intention-to-treat efficacy and safety analyses were done as originally and prospectively defined in the study protocol. Because of the registrational nature of the study, full toxic effects and efficacy data were available, with full validation of all study outcomes with primary source documentation. Central pathology review confirmed invasive disease, nodal involvement, and biomarker status. Although the initial positive efficacy results[20] were reported in 2002 at the recommendation of the independent data monitoring committee, all patients had completed chemotherapy treatment and no crossover to taxane therapy took place in the FAC-treated patients. Few patients have been lost to follow-up (roughly 0·5% per year in each treatment group), which allows for unbiased comparisons for both efficacy and safety. Finally, long-term cardiac outcomes were prospectively sought and assessed with protocol-specified serial left ventricular ejection fraction measurements.

The BCIRG 001 study also has limitations. After completion of study recruitment and chemotherapy treatment of all patients in 2002, in 2005 adjuvant trastuzumab was shown to substantially improve disease-free survival and overall survival results when combined with taxane chemotherapy, which makes our non-trastuzumab results in this HER2-positive population less relevant. All patients in BCIRG 001 received adjuvant anthracycline chemotherapy, but the need for anthracycline chemotherapy in the HER2-non-amplified population is now under intense scrutiny. Analyses of HER2 status in about 5200 patients who participated in eight separate, large, randomised adjuvant trials that compared anthracycline with non-anthracycline chemotherapies show that only women with HER2-positive breast cancers derive incremental efficacy from anthracycline use.[21–26] Furthermore, the incremental benefit of adjuvant anthracycline chemotherapy seems to be confined to those patients who have both *HER2* amplification and DNA amplification of the gene that encodes a molecular target of anthracyclines, topoisomerase 2α.[27–29] Although effective, non-anthracycline adjuvant chemotherapy regimens are available,[30,31] formal prospective assessment of the effects of eliminating adjuvant anthracycline is underway in the HER2-non-amplified breast cancer population (NCT00887536). Furthermore, formal comparison of the TAC regimen with sequential doxorubicin and cyclophosphamide followed by paclitaxel given every 2 weeks with G-CSF is underway (NCT00093795), which will indirectly allow cardiotoxicity assessment of widely used regimens that have so far only been reported with 3-year outcomes.[3] Because of the absence of direct comparisons of widely used adjuvant therapies, including various other sequential anthracycline and taxane regimens, identification of which anthracycline-and-taxane-based regimen provides the best risk-to-benefit ratio is not currently possible.

Contributors

JRM, MM, CV, M-AL (who were members of the steering committee of BCIRG 001), and the representatives of the study sponsor (BHC and KB) conceived and designed the study and supervised all phases of the investigation. JRM, MM, TPie, JR, J-PG, AS, JG, EJ, AW, TF, JH, RC, MRM, JV, TPin, ÁR-L, BC, PW, LP, KL, DW, CP, JCH, and CV participated in data collection. BHC and KB were the sponsor's clinical study representatives for administrative, technical, and material support. MR, VW, and VH were involved in the analysis and interpretation of data, and MR contributed to the implementation of the study and supervision of the sites. JRM and MM wrote the report, with early revision by CV, and sponsor review by BHC, who was the sponsor's medical officer. Statistical expertise was provided by VH. All authors have read and approved the final version. MM, JM, and CV, as principal investigator and cochairs of this study, respectively, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses.

Conflicts of interest

The BCIRG 001 clinical trial was sponsored by Sanofi, who provided funding and drugs, and contributed to the analysis plan. AS received a grant from the Saskatchewan Cancer Agency to participate to the trial. AW has received a research grant from Aventis. ÁR-L received consultancy fees and his institution received a grant from Sanofi. CV's institution received a grant from Sanofi and he personally received travel support to attend study meetings. J-PG received honoraria and travel support from Sanofi to participate in study review activities. JH's institution received a grant from Aventis. JRM and MM received honoraria from Sanofi. BHC and KB are employees of Sanofi. All other authors declare that they have no conflicts of interest.

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