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Sponsor/company:	**sanofi-aventis**	**ClinialTrials.gov Identifier:**	**NCT00174655**
		Study Code:	**RP56976_PR_315**
Generic drug name:	**Docetaxel**	**Date:**	**02 July 2007**

Title of the study **RP 56976 PR 315/ BIG 02-98**	**AN INTERGROUP PHASE III TRIAL TO EVALUATE THE ACTIVITY OF DOCETAXEL, GIVEN EITHER SEQUENTIALLY OR IN COMBINATION WITH DOXORUBICIN, FOLLOWED BY CMF, IN COMPARISON TO DOXORUBICIN ALONE OR IN COMBINATION WITH CYCLOPHOSPHAMIDE, FOLLOWED BY CMF, IN THE ADJUVANT TREATMENT OF NODE-POSITIVE BREAST CANCER PATIENTS** **Sponsor: sanofi-aventis**
Study chairs	**Dr Martine Piccart (IJB, Belgium), John Crown (ICORG, Ireland) and Prudence Francis (IBCSG, Australia**
Participating groups/ country	Nine groups have participated in the trial involving 172 centers and 21 countries: • **Coordinating cooperative** group (countries): **B**reast **E**uropean **A**djuvant **S**tudy **T**reatment Group, **BR.E.A.S.T.** (Belgium, Brazil, Czech Republic, Germany, Israel, Italy, Portugal, Slovakia, South Africa) • **Others groups** (countries): **ABCSG** (Austria), **ANZ-BCTG** (Australia and New Zealand), **DBCG** (Denmark), **GEICAM** (Spain), **GOCCHI** (Chile), **IBCSG** (Hungary, Italy, Spain, Slovenia, Sweden, Switzerland and South Africa), **ICORG** (Ireland) and **SBCG** (Sweden). The number of patients recruited per country (number of patients) was: Australia/ New Zealand (605), Austria (174), Belgium (334), Brazil (87), Chili (67), Czech Republic (27), Denmark (156), Germany (56), Hungary (109), Ireland (190), Israel (82), Italy (169), Portugal (22), Slovakia (31), Slovenia (19), South Africa (115), Spain (240), Sweden (202), Switzerland (143) and UK (59).
Abstract/ publication	The study main analysis results have been presented as oral communication at ASCO 2006, abstract n° LBA159-Author: Pr J. Crown A sub-analysis was performed on CNS relapses, SABCS 2006-poster n°2082- Author Dr B Pestalozzi The Manuscript is under submission to JNCI.
Study design	Prospective, non-blinded, randomized, phase III trial, 4 arms study: control arms (A1, A2) sequential or combined/ concurrent drug administration; experimental arms (B, C) with sequential or combined/ concurrent docetaxel administration. Randomization was unbalanced favouring experimental arms 2:1.

	Sequential Arms: **Combined/ Concurrent Arms** **Arm A1**: 4A ? 3CMF **Arm A2**: 4AC? 3CMF **Arm B**: 3A ? 3T ? 3CMF **Arm C**: 4AT ? 3CMF Treatment duration: Arm A1 and A2: 7 cycles- 24 wks Arm B: 9 cycles -30 wks Arm C: 7 cycles- 24 wks with: A = doxorubicin (75mg/m²), AC = doxorubicin + cyclophosphamide (60/600 mg/m²), T = docetaxel (100mg/m²), AT = doxorubicin + docetaxel (50/75 mg/m²)
Objectives	Primary objectives · To compare disease-free survival (DFS) of an adjuvant treatment with docetaxel given either sequentially or in combination with doxorubicin and followed by CMF to doxorubicin alone or in combination with cyclophosphamide and followed by CMF in operable breast cancer patients with positive axillary lymph nodes (arms B+C) versus (arms A1+A2). Secondary objectives · To compare disease-free survival of an adjuvant treatment with doxorubicin followed by docetaxel followed by CMF to doxorubicin followed by CMF in operable breast cancer patients with positive axillary lymph nodes (B versus A1). · To compare disease-free survival of an adjuvant treatment with docetaxel in combination with doxorubicin followed by CMF to doxorubicin in combination with cyclophosphamide followed by CMF in operable breast cancer patients with positive axillary lymph nodes (C versus A2). · To compare disease-free survival of an adjuvant treatment with doxorubicin followed by docetaxel followed by CMF to doxorubicin in combination with docetaxel followed by CMF in operable breast cancer patients with positive axillary lymph nodes. (sequential mono-chemotherapy versus polychemotherapy) (B versus C). · To compare overall survival of treatment arms. · To compare toxicity of treatment arms. · To evaluate pathologic and molecular markers for predicting efficacy: in parallel to the clinical part, tumour samples were collected. Key-biological markers will be evaluated at study end. · Socioeconomic data will be collected in order to be able to perform a socioeconomic analysis by country, when needed.
Dosage regimen	Patients were post-surgically stratified at inclusion according to participating center, number of axillary lymph nodes involved (1 to 3; 4 and more), age (< 50; > 50), and were randomly assigned to receive either: -**Arm A1**: doxorubicin 75 mg/m² i.v. day 1 q 21 days for 4 cycles, followed by CMF (C: cyclophosphamide 100 mg/m² orally days 1-14, M: methotrexate: 40 mg/m² i.v. days 1 and 8, FU; 5-fluorouracil: 600 mg/m²) i.v. days 1 and 8, q 28 days) for 3 cycles. -**Arm A2**: doxorubicin 60 mg/m² i.v. + cyclophosphamide 600 mg/m² i.v., day 1, q 21

	days for 4 cycles, followed by CMF (as above) for 3 cycles. -**Arm B**: doxorubicin 75 mg/m² i.v. day 1, q 21 days for 3 cycles, followed by docetaxel 100 mg/m² i.v., 1 hour infusion, day 1, q 21 days for 3 cycles, followed by CMF (as above) for 3 cycles. -**Arm C**: doxorubicin 50 mg/m² i.v. + docetaxel 75 mg/m² i.v. 1 hour infusion (1 hour after doxorubicin), day 1, q 21 days for 4 cycles, followed by CMF (as above) for 3 cycles. Actual body weight was used to calculate body surface area (BSA) and after an amendment, BSA was capped at 2.0 m^2. **Clinical, haematological and biochemical assessments** were required prior to each cycle, including assessment of toxicities according to NCI-Common Toxicity Criteria version 2. The first cycle should be administered within 8 days following the randomization date. Treatment cycles were commenced if neutrophil counts were $\geq$ 1.5 x 10^9/L and platelets $\geq$ 100 x 10^9/L. If neutrophils were $\geq$ 1.0 x 10^9/L and platelets $\geq$ 100 x 10^9/L on day 8, CMF was administered on day 8-14. Dose-reduction and/or treatment delay and treatment discontinuation were planned for the 4 arms in case of severe hematological and/or non hematological toxicity. Dose reductions of 20-25% were required for the specific drug or drug combination in case of severe ($\geq$ grade 3) non-hematologic toxicity (eg combination AT 50/75 mg/m^2 reduced to 40/60 mg/m^2; single agent docetaxel 100 mg/m^2 reduced to 75 mg/m^2). If oral cyclophosphamide could not be tolerated during CMF, a switch to iv cyclophosphamide at a dose of 600 mg/m2 iv on days 1 + 8 was allowed. **Hormonotherapy (for Arms A1, A2, B and C)**: - Tamoxifen was the recommended hormonotherapy and should be administered as 20 mg p.o. daily for 5 years, starting 4 to 5 weeks after day 1 of the last course of chemotherapy, in patients with ER and/or PgR positive tumors biochemical or immunohisto-chemical methods required; ER and/or PgR positivity should be in accordance with the policy in use at each participating center. Each center specified its own policy. -Anastrozole 1 mg p.o. daily was an alternative in hormone receptor positive, postmenopausal patients if used consistently with the country-specific label. Postmenopausal women with hormone receptor positive tumours with a high risk recurrence were reasonable candidates for the inclusion of an aromatase inhibitor in their adjuvant treatment plan (early sequence with exemestane 25 mg p.o. daily for 3 or 2 years after 2 or 3 years of tamoxifen, or late sequence with letrozole 2.5 mg p.o. daily for 5 years after 5 years of tamoxifen). Ovarian ablation/suppression (oophorectomy or GnRH agonists) in combination with tamoxifen was allowed for hormone receptor positive premenopausal women. While 5 years of tamoxifen is the standard treatment, other types or durations or combinations of endocrine treatment as alternatives to or in addition to tamoxifen should be allowable according to investigator's preference. However, duration of at least 5 years of adjuvant hormonal therapy was recommended. In post menopausal women the use of aromatase inhibitors (eg anastrazole 1mg po daily, exemestane 25 mg po daily or letrozole 2.5 mg po daily) was allowed. In premenopausal women,

	ovarian ablation (eg oophorectomy or radiation) or ovarian suppression (eg GnRH agonists) were allowed in addition to Tamoxifen for 5 years. In any case, use of additional hormonal treatments had to be recorded. **Radiotherapy: (for Arms A1, A2, B and C)** Radiotherapy was mandatory in case of breast-conservative surgery; allowed in case of mastectomy, according to the policy in use at each participating center. Each center specified its own policy before study activation. Radiotherapy began 4 to 6 weeks after day 1 of the last course of CMF. Concomitant CMF and radiotherapy were allowed although not recommended.
Prophylactic regimens Medication, Dose & Route Schedule	**Steroids (only for Arms B and C during treatment with docetaxel)** · Dexamethasone 8 mg i.v. or i.m. or orally, or · Methylprednisolone 40 mg i.v. or i.m. or 32 mg orally, or · Prednisone 50 mg i.v. or i.m. or orally, or · Prednisolone 50 mg i.v. or i.m. · or other equivalent for 6 doses 1. night before chemotherapy (- 12 h) 2. morning of chemotherapy (- 3 h) 3. 1 hour before docetaxel infusion (- 1 h) 4. night of chemotherapy (+ 12 h) 5. morning the day after chemotherapy (+ 24 h) 6. evening the day after chemotherapy (+ 36 h) **Antibiotics (only for Arm C during treatment with AT)** Patients treated according to arm C would receive a prophylactic antibiotic regimen consisting of ciprofloxacin 500 mg orally twice daily, from day 6 to day 12 (inclusive) of each cycle of AT. **No primary prophylaxis with G-CSF** was permitted, however G-CSF was recommended after subsequent doses of doxorubicin and/or docetaxel, if treatment delay of > 7 days occurred due to neutropenia or prior febrile neutropenia or grade 3 - 4 infection. If these problems recurred despite G-CSF, then dose reduction was required.
Sample size and Study timelines	2730 patients were to be included as per protocol (910 patients per arm in the experimental arms B and C and 455 patients per arm in control arms A1 and A2). Enrolment was planned to start in April 1998 and to be completed on June 2001. The first patient was included on June 10, 1998 and 2887 patients were randomized (Arm A1: 481: A2: 487; B: 960 and C: 959 patients). The inclusion period was closed on July 1st, 2001. Patient should be followed during 10 years and two interim analyses were planned at 405 and 810 events. The first interim efficacy analysis was performed after 395 events, and study continuation was recommended by the IDMC. By September 2003, it was evident that the overall event rate was much lower than anticipated, hence the time to the second interim analysis (810 events) and main analysis (1215 events) would occur much later than planned. After consultation with IDMC, an amendment to the study

	plan was adopted (amendment n°4), in which the main analysis would occur after a median follow-up of 5 years or after 810 events, whichever occurred first. The main analysis would use a one- sided significance level of 0.0248 The data base was locked on March 22, 2006 and the study results presented as oral communication at ASCO 2006. Further updated analyses are planned in 2008 and 2010
Inclusion criteria	Inclusion criteria were: 1) Written or witnessed informed consent prior to begin specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements. The Helsinki declaration of human rights must be the basis for inclusion of patients. 2) Histologically proven breast cancer. Interval between definitive surgery that includes axillary lymph node dissection and registration must be less than 60 days. A representative sample of the primary tumor (either blocks or slides) must be sent to the operational office, for central pathology reviews, after patient's randomization. 3) Definitive surgical treatment must be either mastectomy or breast conserving surgery, with axillary lymph node dissection (not sampling) for operable breast cancer (clinical T1-3, N0-1, M0). Margins of resected specimen from definitive surgery must be histologically free of invasive adenocarcinoma and ductal carcinoma in situ (DCIS). Lobular carcinoma in-situ does not count as a positive margin. Patients with histologically-documented infiltration of the skin (pT4) will not be eligible. Patients who have a breast conserving procedure with a positive margin may become eligible if they subsequently undergo adequate resection or mastectomy with clear margins. 4) Histologic examination of the tumor: invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of eight resected lymph nodes. All nodes must be examined by the pathologist. The determination of ER (estrogen receptor) and PgR (progesterone receptor) is mandatory and results must be known by the end of chemotherapy in order to decide whether hormonal therapy is indicated 5) Age $\geq$ 18 years and age $\leq$ 70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for women > 70 years of age. 6) Karnofsky Performance status index $\geq$70 % 7) Normal cardiac function must be confirmed by LVEF (MUGA scan or echocardiography). The result must be above the lower limit of normal for the institution. 8) Laboratory requirements: (within 14 days prior to registration) a) Hematology i) Neutrophils $\geq 2.0 \times 10^9$/L ii) Platelets $\geq 100 \times 10^9$/L iii) Hemoglobin $\geq$10 g/dL b) Hepatic function i) Total bilirubin $\leq$ 1 UNL ii) ASAT (SGOT) and ALAT (SGPT) $\leq$ 1.5 UNL iii) Alkaline phosphatase $\leq$ 2.5 UNL c) Renal function i) Creatinine $\leq$ 150 µmol/L (1.5 mg/dL) ii) If creatinine is borderline, the calculated creatinine clearance should be $\geq$ 60 mL/min (Cockcroft formula).

	9) Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest X-ray (PA and lateral) and/or CT-scan, abdominal ultrasound and/or CT scan, bone scan (in case of positive bone scan suspicious for metastases, bone X-ray (or bone CT-scan for spine) on hot spots is mandatory to rule out the possibility of metastatic hot spots). Other tests may be performed as clinically indicated. 10) Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at a participating center which could be a Principal or a co-investigator's site. In case patient moves during the follow-up, every effort should be done to follow the patient in a participating center. 11) Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential. Patients of childbearing potential must implement adequate non-hormonal measures to avoid pregnancy during study treatment (chemotherapy, radiotherapy and hormonal therapy).
Exclusion criteria	Exclusion criteria were: 1) Prior systemic anticancer therapy for breast cancer (chemo-immuno-hormonotherapy). 2) Prior radiation therapy for breast cancer. 3) Pregnant, or lactating patients. 4) Any locally advanced (clinical or pathological T4 and/or N2-known N3) or metastatic (M1) breast cancer. Patients with inoperable residual axillary nodal disease or with supraclavicular nodes. 5) Pre-existing motor or sensory neurotoxicity of a severity $\geq$ grade 2 by NCI criteria. 6) Other serious illness or medical condition: a) congestive heart failure or unstable angina pectoris, previous history of myocardial infarction within 1 year from study entry, uncontrolled hypertension or high-risk uncontrolled arrhythmias b) history of significant neurologic or psychiatric disorders including psychotic disorders, dementia or seizures that would prohibit the understanding and giving of informed consent c) active uncontrolled infection d) active peptic ulcer, unstable diabetes mellitus 7) Past or current history of other neoplasms except for: a) curatively treated basal cell skin cancer b) adequately treated in situ carcinoma of the cervix In regard to past or current history of other breast carcinoma, criteria of exclusion are: a) past history of ipsilateral or past or current history of contralateral invasive breast carcinoma b) past or current history of contralateral ductal in situ breast carcinoma A past or current history of ipsilateral ductal in situ or lobular in situ (ipsilateral or contralateral) breast carcinoma is not a criterion of exclusion. 8) Chronic treatment with corticosteroids unless initiated > 6 months prior to study entry and at low dose ($\leq$20 mg methylprednisolone or equivalent). 9) Concurrent treatment with hormonal replacement therapy. Prior treatment should be stopped before study entry. 10) Definite contraindications for the use of corticosteroids. 11) Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.

	12) Concurrent treatment with any other anti-cancer therapy. 13) Male patients.
Study Amendment	The study was amended four times**:** - amendment n°1 (Dec 17, 1999)**:** add a second interim analysis and perform both interim analyses prompted by the number of events - amendment n°2 (Dec 1, 2000): closed testing procedure to handle multiplicity, update the clinically relevant difference, - amendment n°3 (Aug 21, 2002): to make clarifications and review the statistical plan, - amendment n°4 (Nov 18, 2004): the second interim analysis becomes the main analysis using significance level of 0.0248
Efficacy evaluation	• An intention to treat (ITT) analysis was to be conducted for all randomized patients. In addition, an analysis was to be conducted among the eligible patients • Disease-Free Survival (DFS) was defined as the interval from the date of randomization to the date of local, regional or metastatic relapse or the date of second primary cancer or death from any cause whichever occurs first. • Survival was measured from the date of randomization up to the date of death of any cause.
Statistical considerations	**Sequential Arms**: **Arm A1**: 4A ? 3CMF **Arm B**: 3A ? 3T ? 3CMF **Combined/ Concurrent Arms** **Arm A2**: 4AC? 3CMF **Arm C**: 4AT ? 3CMF Considering that the DFS of the control groups (A1 and A2) was supposed to be around 50 % at 5 years, it was expected that the addition of docetaxel in the adjuvant treatment would increase the DFS at 5 years of 8.3 % (from 50 % to 58.3 %). The following comparisons were of interest to assess the activity of docetaxel and to compare poly-chemotherapy versus sequential mono-chemotherapy: **Primary comparisons**: (B+C) versus (A1 + A2) power 99%, no. of pts: 1820 vs 910 The original sample size was 2200 and control patients were expected to have a 5 year DFS of 50%. An absolute increase of 10% in DFS at 5 years was considered a clinically meaningful difference. The sample size was calculated to have sufficient power to detect a clinically relevant difference in both the primary and secondary comparisons. In December 2000 with the approval of the Independent Data Monitoring Committee (IDMC) and subsequent to the FDA approval of paclitaxel for node positive breast cancer, the study plan was amended. A 22% decrease in the risk of relapse in favor of the experimental (docetaxel) arms was deemed a clinically relevant difference, and the sample size was increased to 2730. The primary comparison to be carried out evaluated the role of docetaxel regardless of its mode of administration: (sequential docetaxel + concurrent docetaxel) versus (sequential control + concurrent control). This comparison would have a power of 99% to detect a clinically relevant difference with a one-sided log rank test using a significance level of 0.025. The study analysis was to be performed using a Closed Testing Procedure principle to protect the overall type I error.

	Secondary comparisons : B versus A1 power 85% to detect a clinically relevant difference no. of pts: 910 vs 455 C versus A2 power 85% to detect a clinically relevant difference no. of pts: 910 vs 455 B versus C power 86% to meet equivalence (two-sided 95% confidence interval of the hazard ratio [0.80; 1.25]) no. of pts: 910 vs 910 Overall no. of pts = 2730 The secondary individual comparisons of sequential docetaxel versus sequential control and concurrent docetaxel versus concurrent control would each have a power of 85% to detect a clinically relevant difference with a one-sided log rank test, using a significance level of 0.025. The comparison of docetaxel administered sequentially following doxorubicin versus concurrently would be performed by calculating the 95% confidence interval of the hazard ratio. Additional secondary objectives of the trial were to compare the overall survival (OS) and toxicity of the treatment arms and to evaluate pathologic and molecular markers In order to handle the multiplicity issue induce by the study design, a decision tree based on the Closed Testing Procedure principle was to be used in order to protect the overall type I error. The first interim efficacy analysis was performed after 395 events and study continuation was recommended by IDMC. By September 2003, it was evident that the overall event rate was much lower than anticipated, hence the time to second main analysis (810 events), 8 year and 10 year follow-up descriptive analysis (1215 and 1500 events) would occur later than planned. After IDMC consultation an amendment to the study plan was adopted (amendment n°4) in which the main analysis would occur after a median follow-up of 5 years or after 810 events, whichever occurred first. The main analysis would use a one-sided significance level of 0.0248.
Study Results	The RP 56976-V-315 or BIG 02-98 trial was designed to test if incorporating docetaxel could improve results compared with optimal anthracycline-based adjuvant chemotherapy of a similar duration. It was also designed to assess if docetaxel should optimally be administered sequentially after doxorubicin, or by administering the two drugs concurrently, which requires a dose reduction of each drug. The main analysis was performed at median follow-up of 62.5 months with 732 events (less than two thirds of the 1215 events originally planned). Results of DFS and safety are presented below.

Between June 1998 and June 2001, 2887 women with resected node positive breast cancer were randomized between the four treatments. Baseline characteristics of these patients were well balanced and are listed in Table 1. The median age of women entered was 49 years (range 21-70) and 4% were over 65 years. Mastectomy was performed in 55%, the remainder having undergone breast conserving surgery. Patients had a median of three positive nodes among a median of 16 resected axillary nodes. Almost half (46% patients) had four or more positive nodes. The breast tumour was hormone receptor positive in 76% of patients.

Table 1- Baseline characteristics

Treatment Arm	**Sequential Control Arm A1**	**Concurrent Control Arm Arm A2**	**Sequential Docetaxel Arm Arm B**	**Concurrent Docetaxel Arm Arm C**
	A x 4 → CMF	**AC x 4 → CMF**	**A x 3 → T x 3 → CMF**	**AT x 4 → CMF**
Patients n = 2887	n = 481	n = 487	n = 960	n = 959
Age (Stratification factor) < 50 years ≥ 50 years	 53% 47%	 54% 46%	 53% 47%	 53% 47%
No. positive nodes 1-3 (Stratification factor) 4 or more	 54% 46%	 55% 45%	 54% 46%	 54% 46%
Hormone Receptors ER and/or PR ER and PR negative	 75% 24%	 75% 25%	 75% 24%	 76% 24%
Menopausal status Premenopausal Postmenopausal Other	 55% 38% 7%	 57% 38% 5%	 54% 40% 6%	 58% 37% 5%
Tumor size pT1-2 pT3	 94% 6%	 92% 7%	 93% 6%	 91% 8%
Type of surgery Breast conserving Mastectomy	 46% 54%	 45% 55%	 46% 54%	 44% 56%

Treatment received and dose intensity delivered for chemotherapy treatment is detailed in Table 2. Twenty two randomized women (1.2% of those randomized to control treatment and 0.5% of those randomized to docetaxel) never started their allocated protocol treatment.

Chemotherapy treatment was completed by 93% in sequential control, 94% in both concurrent arms and 91 % in sequential docetaxel arm. Relative dose intensity (RDI) of doxorubicin was 96% in sequential control arm and 97% for concurrent and docetaxel sequential arm. Docetaxel RDI was 95% and 97% in sequential and concurrent arm respectively. CMF RDI was of 92% across the arms.

Adjuvant hormonal therapy was received by 71% patients in sequential control, 74% in concurrent control, 74% in sequential docetaxel and 75% in concurrent docetaxel arm. Radiation therapy was administered respectively to 82%, 81%, 81% and 82% of patients, equally distributed across the treatment arms. Overall 2.8% of patients were lost to follow-up, with equal percentages from control and docetaxel treatment groups

The results showed that dose reductions occurred in 18% patients in the sequential

control arm, 17% patients in the concurrent control arm, 25% patients in the sequential docetaxel arm and 20% patients in the concurrent docetaxel arm.

Table 2 -Treatment administered and Drug Relative Dose intensity

Treament Arm N= 2887 (ITT)	**Sequential Control Arm A1** N=481	**Concurrent Control ArmA2** N= 487	**Sequential Docetaxel Arm B** N= 960	**Concurrent Docetaxel Arm C** N= 959
	A x 4→ CMF	**AC x 4→ CMF**	**A x 3→T x 3→ CMF**	**AT x 4 → CMF**
Started protocol treatment (%)	98 %	99 %	99 %	99 %
Number of cycles Time to complete	7 cycles 24 weeks	7 cycles 24 weeks	9 cycles 30 weeks	7 cycles 24 weeks
Completed protocol treatment	93%	94%	91%	94%
Received hormonal therapy	71%	74%	74%	75%
Received radiotherapy	82%	81%	81%	82%
Lost to follow-up	3%	1%	2%	2%
Doxorubicin relative dose intensity (mean)	96%	97%	97%	97%
Docetaxel relative dose intensity (mean)	--	--	95%	97%
CMF relative dose intensity (mean)	92%	92%	92%	92%

Efficacy results

At the time of this analysis, the median follow-up was 62.5 months and 732 events had occurred (Table 3). The smaller number of events at 5 years was due to a more favourable course for all women in the trial than anticipated.

The most common non-breast second primary malignancies were melanoma, colo-rectal and endometrial. There were 5 cases of leukemia/myelodysplasia with an incidence of 0.3% in control arms and 0.1% in docetaxel treated patients.

Table 3-Patients with first Events

Treatment Arm N= 2887	**Sequential Control Arm A1**	**Concurrent Control Arm A2**	**Sequential Docetaxel Arm B**	**Concurrent Docetaxel Arm C**
	A x4 → CMF	**AC x 4→ CMF**	**A x3→ T x 3 → CMF**	**AT x4→ CMF**
Breast cancer relapse	21.8%	24.8%	19.9%	23.5%
Death	1.5%	0.8%	0.3%	0.6%
Contralateral breast	1.5%	0.8%	0.2%	0.7%
Other 2nd primary	2.1%	1.6%	1.9%	1.5%
Total Events	**26.8%**	**28.1%**	**22.3%**	**26.3%**
Event free patients	**73.2%**	**71.9%**	**77.7%**	**73.7%**

Results of the primary and secondary comparisons are shown in Table 4. The primary comparison evaluated the incorporation of docetaxel, regardless of its mode of administration, into anthracycline-based cross-over adjuvant chemotherapy stratified for age and nodal status.

Overall docetaxel resulted in an improvement in DFS for the primary comparison (B+C vs A1+A2) though not statistically significant (HR 0.86; 95% CI = 0.74-1.00, p= 0.051). However the secondary comparisons demonstrated some possibly important differences in efficacy related to the schedule of adjuvant docetaxel in relation to doxorubicin. Docetaxel administered sequentially after doxorubicin (arm B) resulted in superior DFS (HR = 0.79; 95% CI 0.64-0.98; p=0,035) compared to the sequential control arm (arm A1). Docetaxel administered concurrently with doxorubicin (arm C) resulted in a similar outcome to the combined control arm (arm A2).

Table 4-Hazard Ratios for Disease-free Survival

Trial Comparisons	**Patients Per Group**	**Total Patients**	**Comparison**	**Hazard Ratio [95% C.I.] * *P-value***	**F**
Primary comparison Docetaxel vs Control	1919 968	n = 2887	**Arm B**:A→T→CMF + **Arm C**: AT→CMF vs **Arm A1**: A→CMF + **Arm A2** : AC→CMF	0.86 [0.74-1.00] ***0.051***	.(
Sequential Docetaxel vs Sequential Control	960 481	n = 1441	**Arm B:** A→T →CMF vs **Arm A1**: A→CMF	0.79 [0.64-0.98] ***0.035***	.(
Concurrent Docetaxel vs Concurrent Control	959 487	n = 1446	**Arm C**: AT →CMF vs **Arm A2**: AC →CMF	0.93 [0.75-1.14] ***0.48***	.4
Sequential Docetaxel vs Concurrent Docetaxel	960 959	n = 1919	**Arm B**: A→T →CMF vs **Arm C**: AT→CMF	0.83 [0.69-1.00] ***Not planned***	N
Hypothesized HR				0.78	

* Primary analysis , stratified for age and nodal status.

Table 5 details the estimated 5-year DFS for the four treatment arms for all patients and according to hormone receptors, nodal status and age. The control patients overall had a 5-year DFS of 73% which demonstrates the low event rate in this trial. For patients in the sequential docetaxel arm, the estimated 5-year DFS was 78%. Less than 15% of patients with 1-3 involved nodes treated with the sequential docetaxel arm had relapsed at 5 years.

Table 5-Kaplan-Meier Estimates of Five year Disease-free Survival

	Sequential Control **Arm A1** A x4 → CMF	Concurrent Control **Arm A2** AC x 4 → CMF	Sequential Docetaxel **Arm B** A x 3 → T x 3 → CMF	Concurrent Docetaxel **Arm C** AT x 4→ CMF
Patients n = 2887	n = 481	n = 487	n = 960	n = 959
All patients	73.0%	72.4%	78.0%	73.8%
Hormone Receptor +ve	77.0%	77.0%	81.2%	77.8%
Hormone Receptor -ve	61.1%	59.0%	68.2%	60.6%
1-3 nodes	83.6%	79.7%	85.5%	80.8%
≥ 4 nodes	60.5%	63.5%	69.1%	65.6%
< 50 years	74.2%	73.4%	78.9%	73.1%
≥ 50 years	71.6%	71.2%	76.9%	74.7%

With a median follow-up of 62.5 months there were 403 deaths among 2887 patients entered in the study. No significant differences in overall survival (OS) were observed between patients randomized to docetaxel versus control treatments (B+C vs A1+A2; HR= 0.92 ; 95% C.I. 0.75-1.13). The estimated 5-year OS was 90% for patients randomized to receive docetaxel. For patients treated with sequential docetaxel versus concurrent docetaxel (B vs C), the hazard ratio for OS was 0.80 (95% C.I. 0.63-1.02). Given the relatively small number of deaths, additional follow-up is required to ascertain whether significant differences in survival will emerge.

Safety

The percentage of patients experiencing grade 3-4 toxicities and all grades are shown in Table 6. In sequential and concurrent control arms, 25.6% and 27 % of patients had at least one grade 3-4 or another severe or life threatening toxicity, respectively. For docetaxel experimental arms, percentages were 37,8 % and 32, 0 % for sequential and concurrent arm with twenty percent of the hospitalisation due to an adverse event. In sequential and combined control arms 17 and 12% of hospitalisation were reported. The higher incidence of grade 3-4 toxicities in sequential docetaxel arm could be possibly explained by the longer treatment duration (9 weeks compared to 7 weeks with the other regimens).

Febrile neutropenia was more common among docetaxel treated patients, occurring in 7.5% patients on sequential docetaxel arm compared with 11.6% patients on concurrent docetaxel arm. G-CSF was administrated as secondary prophylaxis to 15% and 12% of patients in control arms, 22% and 29% of patients in docetaxel experimental arms. This corresponds to 6% of cycles in sequential control arm, 5% of cycles in concurrent control arm, 7% of cycles in sequential docetaxel arm and 12% of cylces in concurrence docetaxel arm. Stomatitis grade 3-4 was reported as 7.1% in the sequential docetaxel treated patients. Severe neuro-sensory toxicity was rare, although grade 1- 2 neurosensory toxicity was frequently reported with docetaxel and was more frequent among patients receiving sequential than concurrent docetaxel (46.3% versus 23.1%). The incidence in control arm was about 12%. The incidence of severe infection was about 6% in both experimental arm and 4 to 5% in control arms. The incidence of grade 3-4 nausea was reported as 9.1 % in the control concurrent arm and about 4 to 5 % in experimental arms. For vomiting, the incidence of grade 3-4 was also more elevated in control concurrent arm (8%) and was about 4-5 % in the others arms.

Among 2865 patients who received chemotherapy treatment, four toxic deaths have been reported due to pneumonia during CMF in sequential control arm, neutropenic sepsis during CMF in sequential docetaxel arm. Two sepsis (one probable and one with cryptococcal meningitis) were reported in concurrent docetaxel arm during AT administration. Two of the deaths occurred in women aged ≥ 60 years including one

with body weight of 117 kg. The protocol was subsequently amended to cap BSA at 2.0 m^2.

Table 6- Incidence of Grade 3/4 Toxicity by patient

Treament Arm	**Arm A1 A x 4→ CMF**	**Arm A2 AC x 4→ CMF**	**Arm B A x 3→T x 3→CMF**	**Arm C AT x 4→ CMF**
Febrile Neutropenia (protocol defined *)	4.9%	3.5%	7.5%	11.6%
Infection	4.9%	3.9%	5.9%	6.4%
Asthenia	3.8%	3.7%	7.4%	5.7%
Edema	0.0%	0.0%	0.1%	0.2%
Stomatitis	5.3%	1.6%	7.1%	4.4%
Nausea	5.5	9.1	4.3	5.3
Vomiting	4.9	8.0	4.4	4 .1
Incidence of all grades per patient (%)				
Diarrhea	31.8	29.5	43.2	39.7
Allergy	6.6	5.6	14.3	14.5
Fever w/o infection	17.2	14.2	25.8	31.5
Infection	44.9	45.4	50.0	41.9
Neurosensory	11.7	12.6	46.3	23.1
Skin	24.4	19.2	40.1	29.7
Stomatitis	65.7	54.6	71.1	67.4
G-CSF use	15%	12%	22%	29%
Hospitalization due to AE	17%	12%	20%	20%
Treatment related deaths	0.2%	0%	0.1%	0.2%

* Protocol defined Febrile Neutropenia = grade 4 ANC, fever > 38 with either hospitalization or antibiotics

Date of report	24 May 2007