AMENDED CLINICAL TRIAL PROTOCOL 6

COMPOUND: Compound

A multicenter phase III randomized trial comparing docetaxel in combination with doxorubicin and cyclophosphamide (TAC) versus 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) as adjuvant treatment of operable breast cancer patients with positive axillary lymph nodes.

STUDY NUMBER: XRP6976D-316

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CLINICAL STUDY DIRECTOR: [redacted]

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Protocol Amendment 1	Date : September 19, 1997
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BREAST CANCER INTERNATIONAL RESEARCH GROUP
B.C.I.R.G.

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS 5-FLUOROURACIL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (FAC) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. TAX 316

Drug Name/Project Number RP 56976-V-316
Protocol Number RP 56976-V-316

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I STUDY SUMMARY

Title of the study	**A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS 5-FLUOROURACIL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (FAC) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. TAX 316**
Objectives	**Primary objective** To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in operable breast cancer patients with positive axillary lymph nodes. **Secondary objectives** To compare overall survival between the 2 above mentioned arms. To compare toxicity and quality of life between the 2 above mentioned arms. To evaluate pathologic and molecular markers for predicting efficacy. An independent socio-economic study will be conducted in parallel with the clinical study.
Study design and dosage regimen	Prospective, non-blinded randomized phase III trial. Patients will be post-surgically stratified at inclusion first according to the participating institution then according to number of axillary lymph nodes involved (1 to 3; 4 and more) and will be randomly assigned to receive either: **TAC:** Docetaxel 75 mg/m² as 1 hour i.v. infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an i.v. bolus and cyclophosphamide 500 mg/m^2 as i.v. bolus on day 1 every 3 weeks. **FAC:** 5-fluorouracil 500 mg/m^2 as an i.v. bolus on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an i.v. bolus and cyclophosphamide 500 mg/m² as an i.v. bolus on day 1 every 3 weeks. Dose reduction and/or treatment delay and treatment discontinuation are planned for the 2 arms in case of severe hematological and/or non-hematological toxicities. **Both Arms** Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there is a contraindication for the use of tamoxifen therapy. **Both Arms** Patients treated with lumpectomy will undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, may be used at the discretion of the treating radiation oncologist. This will be done according to the guidelines at each institution.

<table>
<tr><td>Prophylactic premedication regimen</td><td colspan="2">Patients receiving docetaxel (TAC) will receive the following prophylactic premedication.</td></tr>
<tr><td></td><td>Medication</td><td>Dose, route and schedule</td></tr>
<tr><td></td><td>Dexamethasone (DXM)

or

Methylprednisolone (40 mg) or Prednisone (50 mg) or Prednisolone (50 mg)</td><td>8 mg p.o. for 6 doses
1. night before chemotherapy
2. morning of chemotherapy
3. 1 hour before docetaxel infusion
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy</td></tr>
<tr><td></td><td>Prophylactic antibiotics:
Ciprofloxacin 500 mg p.o. (or alternate)</td><td>twice a day for 10 days starting day 5 of each cycle (TAC)</td></tr>
<tr><td>Number of patients / Enrollment period / Follow-up period</td><td colspan="2">1491 patients (745 TAC / 746 FAC)

Enrollment start (actual): June 1997

Enrollment stop (actual): June 1999

First interim analysis: October 2001

Second interim analysis: September 2003

Final analysis: once 590 DFS events occur

Disease-Free/Overall Survival update: once 700 DFS events occur</td></tr>
<tr><td>Duration of treatment</td><td colspan="2">All included patients in both arms will receive a fixed number of 6 cycles of treatment.

TAC: 6 cycles
FAC: 6 cycles</td></tr>
<tr><td>Selection of patients Inclusion criteria</td><td colspan="2">1 Written or witnessed oral informed consent prior to beginning 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.

2 Histologically proven breast cancer. Interval between definitive surgery that includes axillary lymph node dissection and registration is less than 60 days.

3 Definitive surgical treatment must be either mastectomy, or breast conserving surgery with axillary lymph node dissection for operable breast cancer (T1-3, Clinical 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.</td></tr>
</table>

Inclusion criteria

4 Histologic examination of the tumor: Invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes. At least one paraffin block from the primary tumor and nodes must be submitted to the central operational office ([redacted] Canada) for post-randomization confirmation of diagnosis and molecular studies.
(see Appendix 10).

5 Estrogen and progesterone receptors performed on the primary tumor prior to randomization. Results must be known by the end of chemotherapy in order to decide whether hormonal therapy is indicated.

6 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 the TAC regimen for women >70 years of age.

7 Karnofsky Performance status index $\geq$ 80%.

8 Normal cardiac function must be confirmed by LVEF or shortening fraction (MUGA scan or echocardiography respectively). The result must be above the lower limit of normal for the institution.

9 Laboratory requirements: (within 14 days prior to registration)

a) Hematology:
   i) Neutrophils $\geq 2.0\ 10^9$/L
   ii) Platelets $\geq 100\ 10^9$/L
   iii) Hemoglobin $\geq$ 10 g/dL

b) Hepatic function:
   i) Total bilirubin $\leq$ 1 UNL
   ii) ASAT (SGOT) and ALAT (SGPT) $\leq$ 2.5 UNL
   iii) Alkaline phosphatase $\leq$ 5 UNL
   iv) Patients with ASAT and/or ALAT > 1.5 x UNL **associated** with alkaline phosphatase > 2.5 x UNL are not eligible for the study.

c) Renal function:
   i) Creatinine $\leq$ 175 µmol/L (2 mg/dL)
   ii) If limit values, the calculated creatinine clearance should be $\geq$ 60 mL/min.

10 Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest X-ray (PA and lateral), abdominal ultrasound and/or CT scan, and bone scan. In case of positive bone scan, bone X-ray is mandatory to rule out the possibility of metastatic hot spots. Other tests may be performed as clinically indicated (see appendix 5).

11 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating center which could be the Principal or Co- investigator's site.

12 Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.

Exclusion criteria	1 Prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy). 2 Prior anthracycline therapy or taxoids (paclitaxel, docetaxel) for any malignancy. 3 Prior radiation therapy for breast cancer. 4 Bilateral invasive breast cancer. 5 Pregnant, or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration. 6 Any T4 or N2 or known N3 or M1 breast cancer. 7 Pre-existing motor or sensory neurotoxicity of a severity ≥ grade 2 by NCI criteria. 8 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 9 Past or current history of neoplasm other than breast carcinoma, except for: a) curatively treated non-melanoma skin cancer b) in situ carcinoma of the cervix c) other cancer curatively treated and with no evidence of disease for at least 10 years d) ipsilateral ductal carcinoma in-situ (DCIS) of the breast e) lobular carcinoma in-situ (LCIS) of the breast 10 Chronic treatment with corticosteroids **unless** initiated > 6 months prior to study entry **and** at low dose (≤ 20 mg methylprednisolone or equivalent). 11 Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment should be stopped before study entry. 12 Definite contraindications for the use of corticosteroids. 13 Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry. 14 Concurrent treatment with any other anti-cancer therapy. 15 Male patients.

Efficacy evaluation	• An intention to treat (ITT) analysis will be conducted for all randomized patients. In addition, an analysis will be conducted among the eligible patients. • Disease-Free Survival (DFS) is 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 (see section 8.1.1). • Survival will be measured from the date of randomization up to the date of death of any cause.
Statistical considerations	[redacted]

II INTRODUCTION AND BACKGROUND

2.1 Introduction

Breast cancer is a leading cancer site in women around the world. In Canada, an estimated 18 600 new cases of breast cancer were diagnosed (30.7% of all cancer) with an estimated 5300 deaths from breast cancer(18.8% of all cancer) for the year 1996 [1]. In the United States, 180 200 new cases (30.2% of all cancer sites) and 43 900 deaths (16.5% of all cancer deaths) are estimated for 1997 [2]. In the European community (EC), an estimated 135 000 new cases per year (24% of all cancer cases) and 58 000 recorded deaths per year (18% of all cancer deaths) are reported [3].

Surgery is the main modality of treatment in patients with breast cancer. Surgery and/or radiotherapy can control local-regional disease in the majority of patients. However, more than 60% will ultimately die due to widespread disease [4].

In the past 10 years, adjuvant hormonal or cytostatic treatment has been increasingly used [5]. Ongoing studies show that adjuvant treatment can prolong time to recurrence and probably survival in some subsets of patients [6].

2.2 Role of Systemic Therapy in Adjuvant Treatment of Breast Cancer

Adjuvant systemic therapy is defined as the administration of chemotherapy or hormonotherapy after primary surgery for breast cancer in order to control clinically occult micro-metastases.

2.2.1 Adjuvant Chemotherapy

The efficacy of adjuvant chemotherapy is well confirmed by the 10-year results of the meta-analysis of the Early Breast Cancer Trialists Cooperative Group [7]. In node positive patients, a 30% reduction in the odds of recurrence and an 18% reduction in the odds of death were reported. Survival curves show that 36% of the controls were disease-free at 10 years compared to 44% for the patients treated with adjuvant chemotherapy. These results were particularly seen for patients younger than 50 years of age, however a similar trend was confirmed for older patients.

A number of chemotherapy protocols have shown effectiveness in the adjuvant setting of breast cancer. The most optimal regimen has not yet been identified. Several regimens represent acceptable alternatives [8]. They range from CMF chemotherapy of variations to anthracycline containing regimens such as AC, CAF, FAC, AVCF or FEC [9-15]. Numerous randomized trials have compared CMF regimens or variations to anthracycline containing polychemotherapies including FAC [11], initially developed by the CALGB.

The role of Adriamycin in the adjuvant treatment of breast cancer is still not entirely resolved. The majority of the trials except one [15] do not show a significant survival advantage in using polychemotherapy with Adriamycin. However, in contrast, there are regular reports of a significantly improved disease-free survival, which have prompted many investigators to considering Adriamycin containing regimens, in particular FAC, as standard chemotherapy in adjuvant treatment of node positive breast cancer.

2.2.2 Adjuvant Hormonotherapy

The role of adjuvant hormonotherapy was also addressed by the Early Breast Cancer Trialists Cooperative Group [7]. Although both younger and older patients received some benefit, older patients tended to benefit more from adjuvant tamoxifen than patients younger than 50 years of age. The benefit appeared to be more related to the age than the menopausal status. As well, positive hormonal receptors appeared to be also an important predictive factor.

Patients aged more than 50, treated with tamoxifen, had a significant reduction of odds of relapse and mortality while in younger women there was benefit seen mostly for odds of relapse.

Data also suggests that the duration of treatment with tamoxifen is an important factor and the optimal recommendation is a five year treatment.

2.3 Docetaxel as Monochemotherapy

2.3.1 Phase II Clinical Studies

Nine hundred and twelve patients have been treated in completed North American and European phase II studies (4136 cycles). The data presented here relate to the analysis of these studies performed in July 1994 (data on file RPR). Eight hundred and thirty-three patients (2720 cycles) were evaluable at the 100 mg/m^2 dose.

2.3.1.1 Safety results in phase 2 studies

Hematologic Adverse Events

Neutropenia was the principal toxicity at this dose (91.5% of cycles including 74.6% of grade IV). It was rarely complicated by fever (7.3% of cycles), the median day to nadir was 8 days and the median duration of grade IV was 7 days. First cycles and subsequent cycles had a similar profile of neutropenia.

Febrile neutropenia was observed in 185/833 evaluable patients (22.2%) of whom 129 received antibiotics (15.5% of the treated patients) over 199/2720 cycles (7.3%).

Anemia was reported in 78.1% of cycles but was never grade III or IV.

Thrombocytopenia was sporadic (7.8% of patients).

Non-Hematologic Adverse Events

Table 1 below gives a summary of the incidence and severity of non-hematologic adverse events observed in patients receiving 100 mg/m^2 in the phase II studies. The more clinically significant adverse events are described in greater detail following the table.

Table 1: Incidence and Severity of Main Non-Hematologic Adverse Events in Patients receiving 100 mg/m² in Phase II Studies

Adverse event	Incidence (n=833)		
	Overall (%)	Grade III (%)	Grade IV (%)
Acute Hypersensitivity Reaction (AHSR)	31.0	6.7	0.6
Skin toxicity	64.3	6.4	1.7
Gastro-intestinal			
• Nausea	44.5	4.2	0.4
• Vomiting	28.1	2.3	0.7
• Diarrhea	43.3	2.8	1.3
• Stomatitis	41.3	5.0	0.5
Neurologic			
• Sensory	47.9	3.6	0.0
• Motor	14.0	3.7	0.1
	Overall (%)	Moderate (%)	Severe (%)
Asthenia	68.2	28.0	10.9
Nail disorder	26.3	6.1	2.3
Arthralgia	9.5	3.3	0.1
Myalgia	22.1	7.2	1.0
Mucous membrane disorder	42.7	13.6	3.1
Fluid retention	**46.7**	**22.0**	**9.0**

Fluid retention

Overall, 46.7% of patients experienced fluid retention syndrome, graded mild in 15.8%, moderate in 22% and severe in 8.8%. In the majority of patients (31.6%), fluid retention syndrome was characterized by edema (peripheral, localized, generalized, lymphedema, edema not otherwise specified, pulmonary edema). Associated pleural effusion, weight gain or both were observed in a range of 14.2% to 20%. Pleural effusion alone was seen in only 4.6% of patients. Infrequent manifestations included ascites, pericardial effusion and increased capillary fragility.

The median cumulative dose to onset of first signs of fluid retention was approximately 400 mg/m². However, the median cumulative dose to treatment discontinuation due to signs and symptoms related to fluid retention was 1301 mg/m². A total of 72 of 386 patients (18.6%) with fluid retention discontinued treatment due to this adverse effect.

A retrospective analysis compared the impact of different premedication regimens (no premedication, 5-day, and 3-day corticosteroid) on both fluid retention and overall safety in advanced breast cancer patients treated with docetaxel monotherapy at the recommended dose of 100 mg/m² over 1 hour infusion.

A total of 546 patients who were recruited in 12 studies were analyzed as follows: 76 patients who did not receive any premedication, 92 patients who received 3-day corticosteroid, and 378 patients who received 5-day corticosteroid regimen. The median number of cycles and the median cumulative dose of docetaxel were comparable across the three groups. However, dose reduction was more frequent in the 5-day group (35%) of patients than in 3-day (23%) and in no premedication group (24%). This difference was statistically significant.

This analysis confirms the efficacy of long lasting corticosteroid premedication, either 5-day or 3-day corticosteroid, in comparison to no premedication in reducing the incidence and severity of fluid retention, in delaying its onset and reducing the treatment discontinuation rate due to fluid retention. When the 5-day group was compared to 3-day group, no difference was observed in the incidence and severity of fluid retention, in the median cumulative dose to onset of the first sign and/or symptom of fluid retention and in the median cumulative dose to onset of moderate and/or severe fluid retention (Table 2 and Figure 1).

On the other hand, more patients in the 3-day group (9.8%) than in the 5-day group (2.9%) discontinued docetaxel due to fluid retention. However, in both groups almost all patients discontinued the treatment after 6 cycles and the median cumulative dose to treatment discontinuation was more than 1000 mg/m² (Figure 2). Therefore, the investigator's decision to discontinue the treatment could be more related to the evaluation of the risk/benefit ratio of each patient rather than the severity of the fluid retention. In fact, among the 9 patients in the 3-day group who discontinued the treatment due to fluid retention, only 4 had a severe fluid retention and the other 5 patients experienced either a mild (1 patient) or moderate fluid retention (4 patients).

Table 2: Fluid retention characteristics

Number of patients n = 546	No premed. n = 76	5-day n = 378	3-day n = 92	p value 5-day vs. 3-day	p value 3-day vs. none
•Median number of cycles (range)	5 (1 - 13)	6 (1 - 24)	6 (1 - 19)		
•Median cumulative dose (range) mg/m²	491 (99 - 884)	527 (5 - 1804)	528 (99 - 1895)		
•Overall incidence by patient	**81.6%**	**56.1%**	**64.1%**	**0.20°**	**0.02°**
Mild	25.0%	25.7%	30.4%		
Moderate	34.2%	23.3%	27.2%		
Severe	**22.4%**	**7.1%**	**6.5%**	**1.0°**	**0.003°**
• Median dose to onset (range) mg/m²	**322.2**	**413.0**	**399.1**	**0.39°°**	**0.03°°**
• Median dose to onset of moderate /severe fluid retention (range) mg/m²	**489.7**	**752.1**	**818.9**	**0.72°°**	**0.001°°**
• Discontinuation:					
No. of patients	**34.2%**	**2.9%**	**9.8%**	**0.007°**	**‹0.001°**
Median dose mg/m²	620.5	NA	1021.8	**0.02°°**	**‹0.001°°**
• Median reversibility (from last infusion to stop date) weeks	17.3	20.0	16.4		
censored data**	51.6 %**	58.0 %**	44.1 %**		

** *No information available for fluid retention resolution*
° *Fisher's exact test*
°° *Logrank test*

Figure 1: Kaplan-Meier curve. Cumulative dose to onset of moderate/severe fluid retention during treatment period

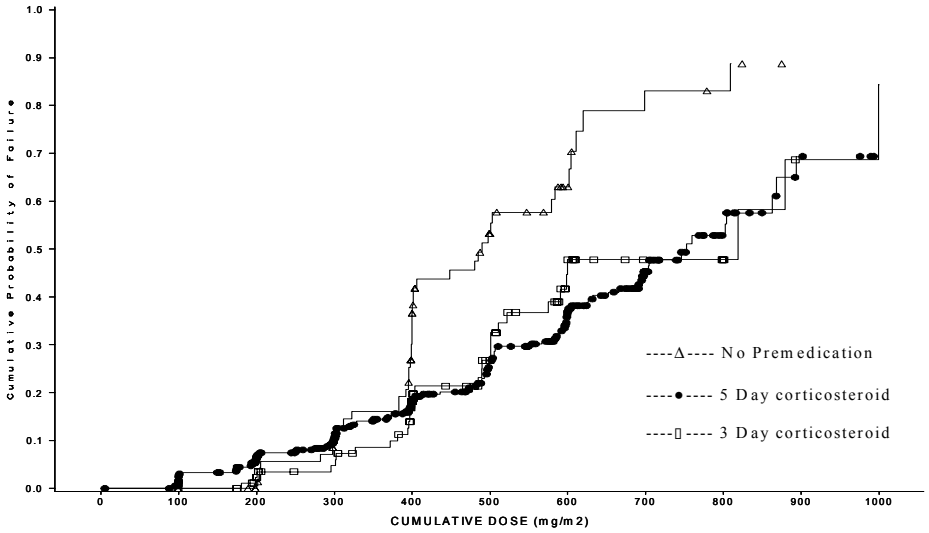
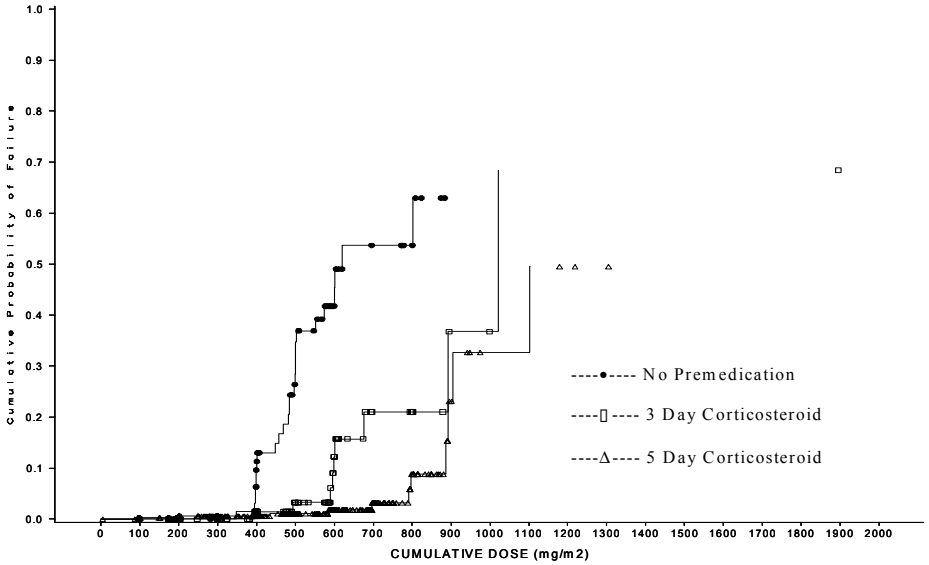


Figure 2: Kaplan Meier curve. Cumulative dose to treatment discontinuation



According to these results, the original recommended premedication (5-day corticosteroids) can be shortened and a 3-day steroid can be recommended to the patients receiving docetaxel.

Table 3: Infection and major non-hematological toxicities

	No premed. N = 76 N (%)	5-day steroid N = 378 N (%)	3-day steroid N = 92 N (%)	p value 5-day vs 3-day	p value 3-day vs None
by patient					
• Any	18 (23.7)	109 (28.8)	16 (17.4)	0.03	0.34
• Grade III	1 (1.3)	27 (7.1)	2 (2.2)		
• Grade IV	1 (1.3)	8 (2.1)	3 (3.3)		
• Grade III/IV	2 (2.6)	35 (9.3)	5 (5.4)	0.30	0.46
Arthralgia-Myalgia	14 (18.4)	84 (22.2)	34 (37.0)	0.005	0.01
• Any	0 (0.0)	13 (3.4)	1 (1.1)	0.32	1.0
• Severe					
Diarrhea					
• Any	38 (50.0)	184 (48.7)	23 (25.0)	< 0.001	0.001
• Grade III/IV	3 (3.9)	31 (8.2)	1 (1.1)	0.01	0.33
Stomatitis					
• Any	35 (46.1)	224 (59.3)	44 (47.8)	0.06	0.88
• Grade III/IV	2 (2.6)	43 (11.4)	1 (1.1)	0.001	0.59

Acute Hypersensitivity Reaction (AHSR)

The overall incidence of AHSR by patient (whatever the premedication) was 31.3%, with 7% grade III and 0.6% grade IV. The incidence of AHSR by cycle was 16.1%, with 3.2% grade III and 0.2% grade IV. At the initial planned dose of 100 mg/m², 0.5% of patients (4 patients) discontinued the treatment prematurely at cycle 1 due to AHSR. Only one of these events was of NCI grade III and considered serious by the investigator.

Among the patients with AHSR, 49.6% experienced it at the first infusion and 40.1% at the second infusion. The most frequent symptoms observed by patients in decreasing order of frequency were: flushing, dyspnea, chest tightness, pain, facial flushing, hypertension and rash. Shortness of breath and pruritus were less frequent. Severe symptoms such as bronchospasm and hypotension were rare.

Skin reactions

The most frequent cutaneous events observed were, in decreasing order of frequency: erythema, pruritus, dry skin, eruption (macula), swelling, burning and desquamation.

The overall incidence by patient (on 833 patients) was 64.3%, with 8.2% grade III to IV. The severity, whatever the premedication regimen used at cycle 1, was between 7.3% and 8.8% at grade III to IV.

Safety analysis in patients with increased liver enzymes

In the population pharmacokinetics (PK) analysis performed in phase II studies, patients with increased transaminases (ASAT and/or ALAT > 1.5 x upper normal limit (UNL) and alkaline phosphatase (Alk. Phos.) > 2.5 x UNL) had a reduction of docetaxel clearance by 27%. Therefore, in order to determine the impact of abnormal baseline levels of liver enzymes on the safety profile of docetaxel, a retrospective analysis was performed independently of the population PK. It appears from this analysis that the subgroup of patients with transaminases >1.5 x UNL and Alk. Phos. > 2.5 x UNL (37 patients) compared to the subgroup with ALAT and/or ASAT ≤ 1.5 x UNL and Alk. Phos. ≤ 2.5 x UNL (775 patients), seems at higher risk of developing severe side effects, higher rate of toxic death and treatment discontinuation after the first cycle as shown in the table 4 below:

Table 4: Incidence of main events observed at first cycle

Group	1	2	3	p value		
Parameters	**T > 1.5 x N & AL > 2.5 x N n (%)**	**T > 1.5 x N & AL ≤ 2.5 x N n (%)**	**T ≤ 1.5 x N & AL ≤ 2.5 x N n (%)**	**1 *vs.* 2**	**1 *vs.* 3**	**2 *vs.* 3**
Number of patients	37 (4.3)	58 (6.7)	775 (89.1)			
Liver metastasis	37 (100.0)	42 (72.4)	216 (27.9)			
Line of docetaxel chemotherapy:						
First line	23 (62.2)	26 (44.8)	472 (60.9)			
Second line	14 (37.8)	32 (55.2)	303 (39.1)			
Discontinuation after first cycle	11 (29.7)	5 (8.6)	53 (6.8)	0.007	0.001*	0.59
Reason: Adverse event	2 (5.4)	0 (0.0)	4 (0.5)	0.15*	0.03*	1*
Toxic death	4 (10.8)	0 (0.0)	4 (0.5)	0.02*	0.001*	1*
Dose reduced at the second cycle	10 (38.5)	12 (22.6)	118 (16.4)	0.14	0.007*	0.24
Febrile neutropenia grade 4 at first cycle	7 (18.9)	14 (24.1)	61 (7.9)	0.55	0.03*	0.0003*
NCI toxicity grade 3 & 4 at first cycle:						
Infection	5 (13.5)	0 (0.0)	18 (2.3)	0.008*	0.003*	0.63
Skin	3 (8.1)	1 (1.7)	17 (2.2)	0.30*	0.06*	1*
Nausea	2 (5.4)	1 (1.7)	12 (1.5)			
Vomiting	1 (2.7)	0 (0.0)	11 (1.4)			
Diarrhea	2 (5.4)	3 (5.2)	17 (2.2)			
Stomatitis	4 (10.8)	4 (6.9)	23 (3.0)	0.71*	0.03*	0.11*
AHSR	4 (10.8)	1 (1.7)	17 (2.2)	0.07*	0.01*	1*
Severe non-NCI toxicity at first cycle:						
Asthenia	3 (8.1)	3 (5.2)	21 (2.7)	0.67*	0.09*	0.23*
Myalgia	1 (2.7)	0 (0.0)	4 (0.5)			

**: Fisher's exact test T: SGOT/SGPT AL: Alkaline phosphatase*

It is to be noted that when only ALAT and/or ASAT were > 1.5 x UNL, the incidence of febrile neutropenia was significantly higher than in the group with normal liver function tests. For all the other safety parameters analyzed no difference was found between patients with ALAT and/or ASAT increased and patients with normal liver function tests.

Additionally, it was noted that the presence of liver metastases in the absence of liver dysfunction does not result in a higher risk of developing severe side effects.

Those results are valid up to the upper range (90th percentile) of data available in the current database i.e. 3 to 3.5 X UNL for ASAT and ALAT and 6 x UNL for Alk. Phos. and normal serum bilirubin levels.

As a consequence of this analysis, all protocols with docetaxel will exclude patients at a high risk of severe side effects until further recommendations could be given from prospective trials in impaired liver function patients.

Serious adverse events

A total of 17 drug-related fatal adverse events (1.9%) were reported. The cause of death was infection in 14 cases (1.5%) (neutropenic infection or pneumonia or sepsis). The three remaining deaths were:

- Gastrointestinal hemorrhage due to docetaxel related thrombocytopenia with concomitant coagulation disorder due to extensive malignant disease involving the liver in a patient with breast cancer.
- Cardiac failure due to pulmonary edema in a patient with non-small cell lung cancer who had a history of aorto-iliac bypass and diabetes mellitus.
- Hemiparesis and drowsiness leading to a possibly docetaxel related death at home in a patient with metastatic malignant melanoma.

2.3.1.2 Human Antitumor Activity

Efficacy of Docetaxel in advanced breast cancer

In the seven European and American phase II breast cancer studies of docetaxel, 283 patients received a total of 1540 cycles. Two patient populations were identified: all treated patients (intention to treat population) and patients who met all eligibility and evaluability criteria called for by the study protocols (evaluable patients). In addition, intention to treat patients were analyzed with regards to having been previously untreated (117 patients) or previously treated (111 patients). A separate analysis was performed on 83 anthracycline resistant patients.

In the population of patients evaluable for response, the overall response rate (ORR) was 58.1% (95% confidence interval (CI) 48.7 to 67.5) for previously untreated patients and 57.1% (95% CI 46.3 to 67.5) for previously treated patients. For those evaluable patients who were anthracycline resistant or refractory, the ORRs were 55.9% (95% CI 43.3 to 67.9) and 46.3% (95% CI 30.7 to 62.6), respectively. There were 10 CR (9.4%) in previously untreated patients and 4 complete response (CR) (4.4%) in previously treated patients.

The duration of response was 30 weeks (range 10 to 69+) in previously untreated patients and 28 weeks (range 3 to 66+) in previously treated patients. Median time to first response was 9 weeks in previously untreated patients and 12 weeks (range 3 to 28+) in previously treated patients. Median time to progression was 21 weeks (range 2 to 69+) in previously untreated patients and 19 weeks (range 2 to 66+) in previously treated patients. Median survival was 15 months for previously untreated patients and 11 months for previously treated patients.

The efficacy results of docetaxel 100 mg/m^2 in breast cancer are summarized in Table 5.

Table 5: Efficacy of Docetaxel 100 mg/m² in Advanced Breast Cancer

	PREVIOUSLY UNTREATED	PREVIOUSLY TREATED	ANTHRACYCLINE RESISTANT	ANTHRACYCLINE REFRACTORY
Number of Patients:				
• **Treated**	117	111	83	49
• **Evaluable**	105	91	68	41
ORR (%):				
• **Intent to treat**	56.4	48.6	48.2	38.8
• **95% CI**	47.4 - 65.4	39.4 - 57.9	37.1 - 59.4	25.2 - 53.8
• **CR**	9.4	3.6	3.6	6.1
ORR (%):				
• **Evaluable**	58.1	57.1	55.9	46.3
• **95% CI**	48.7 - 67.5	46.3 - 67.5	43.3 - 67.9	30.7 - 62.6
• **CR**	9.5	4.4	4.4	7.3
Duration of Response (weeks)	30	28	27	28
range	(10-69+)	(3-66+)	(9-66+)	N/A
Response by metastatic site:				
• **Visceral**	42/78 (54%)	38/69 (55%)	26/49 (53%)	12/28 (43%)
Liver	25/42 (60%)	17/36 (47%)	10/25 (40%)	N/A
Lung	7/22 (32%)	12/19 (63%)	10/15 (67%)	N/A
• **Non-visceral**	19/27 (70%)	14/22 (64%)	12/19 (63%)	7/13 (54%)
Response by number of organs involved:				
• **1**	15/19 (79%)	13/19 (68%)	10/14 (71%)	9/12 (75%)
• **2**	21/40 (53%)	15/29 (52%)	11/20 (55%)	5/10 (50%)
• **>2**	25/46 (54%)	24/43 (56%)	17/34 (50%)	5/19 (26%)
Response by performance status:				
• **0-1**	53/84 (63%)	43/74 (58%)	32/55 (58%)	15/30 (50%)
• **2**	7/15 (47%)	9/17 (53%)	6/13 (46%)	4/11 (36%)
Response by age:				
• **< 50**	25/40 (63%)	22/43 (51%)	18/31 (58%)	9/18 (50%)
• **≥ 50**	36/65 (55%)	30/48 (63%)	20/37 (54%)	10/23 (44%)
Median TFR (weeks)	9	12	9	13
Median TTP(weeks)	21 (2-69+)	19 (2-66+)	19 (2-66+)	18 (2-66+)
Survival (months)	15	11	10	9
RDI	0.91	0.87	0.84	0.87

N/A = not available, CR = Complete Response, ORR= Overall Response Rate, TFR = Time to First Response TTP = Time to progression, RDI = Relative Dose Intensity

2.4 Docetaxel in Polychemotherapy

Phase I Combination Studies with Docetaxel

A large phase I combination studies program has been initiated in several tumor types. In metastatic breast cancer, docetaxel was combined with vinorelbine [16], doxorubicin [17] and with other known active drugs in MBC (cisplatinum, 5 FU i.v. bolus and continuous infusion, cyclophosphamide). From all these studies, the combination of docetaxel with doxorubicin appeared to be the most active.

2.4.1 Phase I Dose Finding Study of Docetaxel and Doxorubicin

2.4.1.1 Introduction and Background

Both docetaxel and doxorubicin have produced a high degree of activity in previously untreated and previously treated patients with metastatic breast cancer. In addition, the remarkable activity of docetaxel in anthracycline resistant disease suggests at least a partial non-cross resistance for docetaxel and doxorubicin and therefore justifies the development of combination chemotherapy to exploit the maximum benefit with the two drugs.

A Phase I dose finding study combining these two agents was conducted at Hôpital Paul Brousse (Villejuif) and at Institut Curie (Paris) from April 1994. At the time of the present report, the study has reached the dose limiting toxicity and is closed for recruitment across all planned dose levels.

The objectives of this Phase I study were:

Primarily, to determine the dose limiting toxicity (DLT), the maximum tolerated dose (MTD) and the recommended dose for phase II and III studies of docetaxel in combination with doxorubicin as first line chemotherapy in metastatic breast cancer patients previously untreated with chemotherapy for metastatic disease.

Secondarily, to assess the safety profile of the combination and the pharmacokinetics of docetaxel when used in combination with doxorubicin.

The main findings of this study follow below.

2.4.1.2 Patients and Methods

Patients

From April 1994 to November 1995, 42 patients with first line metastatic breast cancer were accrued. Inclusion criteria were as follows:

- Metastatic breast cancer
- No prior chemotherapy for metastatic disease. Adjuvant chemotherapy was allowed provided that one year interval had elapsed between the end of adjuvant chemotherapy and study entry. However, to be eligible the patients should have received $\leq$ 300 mg/m² of prior doxorubicin or equivalent dose of epirubicin or THP doxorubicin, except for patients entered at dose level VI (with 60 mg/m² of doxorubicin) when the total permitted dose of prior doxorubicin or equivalent was $\leq$ 200 mg/m².
- WHO PS $\leq$ 2
- Measurable and/or evaluable disease
- Normal baseline left ventricular ejection fraction (LVEF)

Drug administration and prophylactic premedication regimen

- Doxorubicin was administered first as a 15 min i.v. bolus followed after a one hour interval from the end of doxorubicin infusion by docetaxel as one hour infusion.

- This treatment was repeated every 3 weeks on an outpatient basis and without the support of prophylactic granulocyte colony stimulating factors.

- In order to reduce the incidence and severity of fluid retention induced by docetaxel, all treated patients received from their first cycle a prophylactic premedication regimen consisting of 8 mg of oral dexamethasone every 6 hours (starting on day -1 and continued on day 1 and 2), oral Tanakan® (Ginkgo-biloba extract) at a dose of 240 mg/day from study entry until the first symptoms of fluid retention. In addition, they received oral cetirizine (10 mg: 7 and 1 hour before docetaxel) and oral ranitidine (300 mg/day starting on day - 1 and continued for 2 consecutive days).

Dose levels

- The dose levels that were explored during the study are presented in table 5. The starting dose of docetaxel was 50 mg/m² and was increased up to 60, 75 and 85 mg/m². Doxorubicin initial dose was 40 mg/m² and was increased by 10 mg/m² increment up to 60 mg/m².

- The study was completed by the exploration of the combination of docetaxel and doxorubicin both administered at 60 mg/m² q.3.w.

Methodology

At least 3 patients were entered at each dose level. If DLT was observed in one patient out of 3, more patients were included at the same dose level.

- **DLT** was defined as:

  - grade 4 neutropenia lasting more than 7 days,
  - febrile neutropenia lasting more than 3 days,
  - grade 3 to 4 infection and/or grade 4 thrombocytopenia,
  - any other grade 3 to 4 adverse events except anemia.

- **MTD** was considered reached if DLT was observed in > 2 patients out of the 3 entered or in ≥ 3 patients out of the 6 entered.

- All patients were initially evaluated by collection of history, physical examination, complete blood count with liver and renal function tests and electrolytes, chest X-rays bone scan and the all radiological examinations (x-rays, scans and/or ultrasound) to document and assess response. Cardiac monitoring with ECG and LVEF was performed at baseline and then every 2 cycles up to the cumulative dose of doxorubicin of 400 mg/m². At this stage, LVEF was repeated every cycle and the decision whether to continue the treatment or not was based on LVEF results.

- During the treatment, CBC were repeated once every 2 weeks or every 2 days in case of grade 4 neutropenia or febrile neutropenia.

- Response evaluation of measurable and/or evaluable disease was performed every two cycles and using the same method. All patients entered during the study were reviewed by an independent radiologist.

2.4.1.3 Results

Patient characteristics

The main patient characteristics are presented by dose level in Table 6. The median number of organs involved was 3 (1-7). The median WHO performance status (PS) of all treated patients was 0 (0-2) and 67% of patients had visceral involvement. Fifty two percent of patients had received prior adjuvant anthracyclines with a median cumulative dose of 167 mg/m² (67 mg/m² to 247 mg/m²).

Table 6: Dose levels and Patient Characteristics

Dose levels	Doses (mg/m² q3w) A/T	Number of Patients	Age median, (range)	WHO PS median, (range)	Prior Anthra-cyclines. (Patients)	Number of organs involved med. (range)	≤ 2, > 2 (Patients)	Visceral disease (Patients)
I	40/50	3	47, (40-64)	0, (0-0)	3	2, (1-3)	2, 1	2
II	40/60	8	46, (37-65)	0, (0-2)	4	3, (2-6)	2, 6	6
III	50/60	10	50, (41-69)	0, (0-1)	4	3, (1-5)	3, 7	6
IV	50/75	10	46, (34-67)	0, (0-0)	4	2, (2-7)	5, 5	8
V	50/85	5	41, (32-57)	0, (0-0)	4	2, (1-4)	4, 1	4
VI	60/60	6	53, (30-61)	0, (0-0)	3	2, (1-3)	3, 3	2
	TOTAL	42	50, (30-69)	0, (0-2)	22	3, (1-7)	19, 23	28

A = Adriamycin® = doxorubicin, T = Taxotere® = docetaxel, Anthracycline

Tolerance

Overall tolerance

The most relevant safety data observed with this combination are presented in Table 7.

Table 7: Safety Results

Dose levels A/T (mg/m²)	Number of evaluable Patients/ Cycle	Number of Cycles median, (range)	Grade 4 Neutropenia %/Cycle	*Febrile Neutro-penia %/Cycle	Grade 3-4 Infection %/Cycle	Grade 3-4 Mucositis %/Cycle
40/50	3/18	6, (4-8)	11	0	0	0
40/60	8/53	7, (4-9)	77	6	0	0
50/60	10/64	7, (3-9)	75	14	0	0
50/75	10/65	6, (2-10)	92	17	0	0
50/85	5/31	≥6, (6-≥7)	84	6	0**	0
60/60	4/9	≥2, (2-≥3)	100	11	0	0

**Febrile Neutropenia = Grade 4 Neutropenia + Grade ≥ 2 Fever + hospitalization and/or i.v. antibiotics*

*** Two patients with documented infection*

The combination was well tolerated. The median number of cycles administered at all dose levels were always ≥ 6 cycles. Eleven patients continued treatment with single agent docetaxel once the cumulative dose of doxorubicin was reached. As expected with these two hematotoxic drugs, grade 4 neutropenia was frequently observed once the dose of docetaxel was ≥ 60 mg/m². Despite that, only 6% (at 40/60) to 17% (at 50/75) of cycles were complicated by febrile neutropenia requiring i.v. antibiotics or patient hospitalization.

Febrile neutropenia was never life threatening or complicated by grade 3-4 infection.

Anemia and thrombocytopenia were rare.

Grade 3 to 4 nausea, vomiting, diarrhea and, in particular, stomatitis have never been observed.

Fluid retention was usually mild and no patient discontinued treatment due to this adverse event.

More importantly, this combination did not affect the cardiac function. With a median cumulative dose of doxorubicin of 351 mg /m² (240 to 550 mg / m²) reached during the study, neither CHF nor significant LVEF decrease were observed.

Table 8 and Table 9 respectively summarize the median cumulative dose of anthracyclines reached by dose level and the number of patients by range of cumulative dose of anthracyclines.

Table 8: Cardiotoxicity - Incidence of abnormal cardiac function by dose level

Dose levels A/T (mg/m²)	Number of evaluable Patients/ Cycle	Number of Cycles median, (range)	Cumulative dose of doxorubicin (mg/m²) mean, (range)	CHF (Patients)	LVEF decrease (Patients)
40/50	3/18	6 (4-8)	407 (316-514)	0	0
40/60	8/53	7 (4-9)	367 (240-537)	0	1
50/60	10/64	7 (3^+-9)	350 (250^+-550)	0	1
50/75	10/65	6 (2-10)	300 (280-517)	0	2
50/85	5/31	≥6 (6^+-7^+)	≥425 (300-517^+)	0	0
60/60	4/9	≥2 (2^+-3^+)	≥240 (240^+-288^+)	0	0

Table 9: Cardiotoxicity - Incidence of abnormal cardiac function by cumulative dose of anthracyclines

Cumulative dose of doxorubicin (mg/m²)	Number of evaluable Patients	Abnormal cardiac function*	CHF (Patients)	Off study due to cardiotoxicity
≤ 400	26	3	0	No
> 400	16	1	0	No

**Asymptomatic LVEF decrease*

At this time, LVEF decrease not requiring treatment discontinuation was observed in 4 patients: one patient received 5 additional cycles of the combination despite LVEF decrease, doxorubicin alone was discontinued in 2 patients, and the last patient discontinued treatment due to concomitant febrile neutropenia.

Maximum Tolerated Dose and Dose Limiting Toxicity

The MTD of the combination was reached at the fifth dose level with 85 mg/m² of docetaxel and 50 mg/m² of doxorubicin q.3.w. At this dose level, among the five patients evaluable, two have developed a DLT during the first or the second cycle. In addition, febrile neutropenia was observed in 2 other patients.

The Dose Limiting Toxicity was sepsis with positive blood cultures observed in these 2 patients.

Dose reduction at second cycle due to febrile neutropenia and/or its complication was required in 3 patients out of 5 treated at the MTD.

No death was noted during the study.

Activity

Overall response rate, response by type of disease and response by sites are presented in Table 10.

Table 10: Activity - Measurable and evaluable disease

Dose level A/T	40/50	40/60	50/60	50/75	50/85	60/60
Number of Evaluable Patients	**3**	**8**	**9**	**10**	**5**	**4**
ORR						
• Measurable	0/1	3/5	6/7	7/8	2/5	3/3
• Evaluable	1/2	1/3	2/2	2/2	-	1/1
• All	1/3	4/8	8/9	9/10	2/5	4/4
Liver Metastases						
• Measurable	-	2/3	2/2	4/5	2/4	-
• Evaluable	-	0/1	1/1	1/1	-	-
• All	-	2/4	3/3	5/6	2/4	-
Lung Metastases						
• Measurable	-	1/1	0/1	1/1	-	1/1
• Evaluable	1/2	1/1	1/1	1/1	-	1/1
• All	1/2	2/2	1/2	2/2	-	2/2
Soft Tissue Mets						
• Measurable	0/1	2/3	4/4	2/2	1/2	3/3
• Evaluable	0/1	-	2/2	3/3	0/1	-
• All	0/2	2/3	6/6	5/5	1/3	3/3
Visceral Metastases						
• Measurable	-	3/4	2/3	5/6	2/4	1/1
• Evaluable	1/2	1/2	2/2	2/2	-	1/1
• All	1/2	4/6	4/5	7/8	2/4	2/2
Bone Metastases	**0/1**	**2/3**	**3/3**	**4/5**	**1/2**	**3/3**
Number of organs involved						
• ≤ 2	1/2	1/2	3/3	4/5	1/4	2/2
• > 2	0/1	3/6	5/6	5/5	1/1	2/2

Responses were observed at all dose levels, especially at dose levels III (50/60) and IV (50/75) where almost all the treated patients have responded. However, it should be noted that at dose level IV (with 75 mg/m² of docetaxel) among the eight patients with measurable disease, seven have responded and among the six patients with liver metastasis, five patients have responded.

At dose level III (60 mg/m² of docetaxel and 50 mg/m² of doxorubicin), six out of seven patients with measurable disease have responded, however, only two patients had measurable liver disease.

At the last two dose levels explored (85 mg/m² of docetaxel and 50 mg/m² of doxorubicin or 60 mg/m² for both drugs), only 5 and 4 patients were respectively evaluable for response. Therefore, no conclusion could be drawn on the activity of the combination at these two dose levels.

2.4.1.4 Recommended Dose of the Combination

- The Recommended Dose of this combination (defined as the highest and the safest dose of the two drugs when used in combination) is 75 mg/m² of docetaxel and 50 mg/m² of doxorubicin every 3 weeks without the routine support of colony stimulating factors. Indeed, at this dose level, the highest activity of the combination (9 PR/10 and 5 PR among 6 patients with visceral measurable disease) was observed in a representative patient population with metastatic breast cancer and with an acceptable safety profile. In addition, although the 3rd dose level (50/60) has showed a similar activity profile than dose level 4 (50/75), the fourth dose level has been chosen due to the fact that higher dose of docetaxel is given.

- The median relative dose intensity of the combination was always high (>90%) and only 9% of cycles were reduced.

- The safety profile of this dose level is acceptable. Except febrile neutropenia, no grade 3 to 4 non-hematologic toxicity were noted.

2.4.2 Ongoing Studies

A phase II study using the above mentioned recommended doses of docetaxel (75mg/m^2) and doxorubicin (50mg/m^2) in untreated metastatic breast cancer is current ongoing. Fifty patients have been recruited to date. Preliminary data confirms the high antitumor activity and the absence of cardiac toxicity of the combination as shown in the phase I program.

A phase III study comparing docetaxel in combination with doxorubicin (at the dose and schedule defined in the above mentioned phase I program) to doxorubicin in combination with cyclophosphamide is ongoing in Canada, Europe, South Africa, South America, Australia, New Zealand and Israel. As of today, 100 patients have been randomized.

2.4.3 Results of the Pilot Phase II Study of Docetaxel in Combination with Doxorubicin and Cyclophosphamide (TAC)

2.4.3.1 Introduction and Background

Considering the recommended dose of the AT protocol (50/75 mg/m²), it was decided to proceed with a pilot program in untreated metastatic breast cancer aiming at defining a multidrug regimen which could be later randomly compared to a standard doxorubicin containing regimen with equidoses of doxorubin (50 mg/m²) and cyclophosphamide (500 mg/m^2) such as the FAC protocol (5-fluorouracil 500mg/m^2, doxorubicin 50mg/m^2, and cyclophosphamide 500 mg/m²). This represents the rationale for the present study of TAC vs FAC in the adjuvant setting.

The primary objective of this study is the evaluation of the efficacy as measured by response rate, disease free survival and overall survival in patients with metastatic breast cancer treated with a combination of docetaxel, doxorubicin and cyclophosphamide.

The secondary objective is the toxicity profile as measured by the WHO toxicity criteria guidelines.

2.4.3.2 Patients and Methods

This phase II open-label study of docetaxel combined with Adriamycin and cyclophosphamide was performed in patients with metastatic breast cancer. This study has been carried out at the Cross Cancer Institute, Edmonton, Alberta; as well as at the Saskatoon Cancer Centre, Saskatoon, Saskatchewan; Hôpital Sacre-Coeur, Montreal, Quebec; and Tom Baker Cancer Centre, Calgary, Alberta, Canada.

Patient population

Female patients 18 to 70 years old with histopathologically proven metastatic breast cancer.

Patients may have had prior anticancer chemotherapy without anthracycline (doxorubicin or epirubicin) either in the adjuvant or neo-adjuvant setting.

If the patient was estrogen receptor (ER) or progesterone receptor (PR) positive at time of diagnosis, postmenopausal patients must have received at least one hormonal treatment and this treatment must have failed unless hormonal treatment was not appropriate for the patient.

Performance status: Karnofsky index $\geq$ 60%.

Patients must have measurable disease. Measurable disease was defined as bidimensionally or unidimensionally measurable lesions with clearly defined margins on X-ray, CT scan, ultrasound or physical exam. Patients with only blastic bone lesions were ineligible. If disease was only present in the bones, at least 2 lytic lesions were required.

Adequate bone marrow, liver, renal and cardiac functions.

Ability to understand the study and give informed consent.

Treatment

The treatment consisted of:

Doxorubicin:	50 mg/m^2 i.v. followed after a 1 hour interval by
Docetaxel:	75 mg/m^2 i.v. (1 hour infusion)
Cyclophosphamide:	500 mg/m^2 i.v.

One course every three weeks, without G-CSF to a maximum of 8 cycles. Premedication consisted of the same steroid therapy used in the AT regimen and prophylactic antibiotic therapy was systematically prescribed (ciprofloxacin 500 mg p.o. twice a day from day +5 until day +15 following each cycle of TAC chemotherapy).

2.4.3.3 Results

Forty nine patients were accrued so far with 33 patients evaluable for response and 45 patients for toxicity (238 courses).

Patient characteristics were as follows:

Median age: 52 years (34 to 70). The median Karnofsky Index of all treated patients was 90% (80-100). Ten patients (22%) had received prior adjuvant chemotherapy consisting of CMF.

Metastatic sites: The median number of organs involved was 3 (1-6). 64% of patients had visceral involvement. Fifty-three percent of patients presented with bone metastases.

Median follow-up is 7 months (3 to 10).

Efficacy

The major response rate is 85% with complete response in 4 patients (12%) and partial response in 24 patients (73%). Stable disease was seen in 5 patients (15%). There has been no progressive disease seen during the treatment and no progression has been observed so far. The complete response rate must be interpreted taking into account the percentage of patients with bone metastases (53%) for whom the best response was considered partial response despite major osteoblastic reactions while getting extra-skeletal complete responses. In this context, the relative complete response rate is 27%.

Other major outcome parameters including progression-free survival and overall survival are yet to be considered with longer follow-up.

Tolerance

The combination was well tolerated. The mean number of cycles administered was 5.3 cycles with 33 patients having completed the treatment. Twenty two patients have received at least 6 courses and 41 patients have received at least 3 courses delivered so far.

As expected with these three hematotoxic drugs, grade 4 neutropenia (See Table 11) was frequently observed (78%) but was in all cases of short duration (less than 7 days). In order to prevent febrile neutropenia, ciprofloxacin was systemetically prescribed. Among cycles delivered with prophylactic ciprofloxacin, the incidence of febrile neutropenia was 10.8% (21/193) while being 24% for cycles without ciprofloxacin (6/25). The number of hospitalizations secondary to febrile neutropenia was 18/218 (8.2% of courses). The incidence of febrile neutropenia appeared to be more frequent during the first courses of therapy for a given patient and the fact of having had a febrile neutropenia episode does not seem to predict a higher risk of subsequent FN. Febrile neutropenia was never life threatening or complicated by grade 3-4 infection.

Anemia and thrombocytopenia were rare.

Table 11: Safety Results

Number of evaluable Patients/Cycle	Median Number of Cycles (range)	Grade 4 Neutropenia %/Cycle	*Febrile Neutropenia %/Cycle	Grade 3-4 Infection %/Cycle	Grade3 Mucositis %/Cycle
45/218	6 (4-8)	78	12.1	0	1.2

**Febrile neutropenia = Grade 4 Neutropenia + Grade ≥ 2 Fever + hospitalization and/or i.v. antibiotics*

Other extra-hematologic toxicities are summarized in Table 12.

Table 12: Extra-Hematologic Safety Results

% / cycle of 238 evaluable cycles

Adverse event	Grade 0(%)	Grade 1(%)	Grade 2(%)	Grade 3(%)	Grade4(%)
Vomiting	87.9	4.6	6.7	0.8	0
Diarrhea	91.0	3.9	3.9	1.2	0
Mucositis	73.6	18.9	6.3	1.2	0
Pain	74.4	12.2	12.2	1.2	0
Fatigue	66.9	18.0	13.4	1.7	0
Skin	90.4	5.0	4.6	0	0
Neuropathy	81.5	16.0	2.5	0	0
Fluid retention	88.3	5.9	5.4	0.4	0
Allergy	100	0	0	0	0
Cardiac function	89.9	11.1	0	0	0
Nails	100	0	0	0	0

There was no evidence of Grade 4 toxicity. Grade 3 nausea, vomiting, diarrhea and, in particular, stomatitis were rarely seen.

Fluid retention was usually mild and no patient discontinued treatment due to this adverse event. As well, skin toxicity was rare and mild. Allergic reactions were not observed.

More importantly, this combination did not affect the cardiac function. With a median cumulative dose of doxorubicin of 350 mg/m² (140 to 400 mg/m²) reached during the study, no Congestive Heart Failure (CHF) were observed (See Table 13). Five cases of LVEF decrease were seen. They were all Grade I according to Schwartz criteria [18] (LVEF <50% and decrease greater than 10%) and corresponded also to grade I according to NCI common toxicity criteria (asymptomatic decrease of LVEF < 20%). One patient received 3 additional cycles of the combination despite LVEF decrease; doxorubicin alone was discontinued in 1 patient (after 5 courses of TAC), with Taxotere - cyclophosphamide continued without further problem. In 3 cases, a second MUGA scan performed within 1 week following the abnormal test did not confirm the significant decrease and TAC was continued.

Table 13: Cardiotoxicity - Incidence of abnormal cardiac function by cumulative dose of anthracyclines

Cumulative dose of doxorubicin (mg/m²)	Number of evaluable Patients	Abnormal cardiac function*	CHF (Patients)	Off study due to cardiotoxicity
< 350	27	4	0	None
≥ 350	18	1	0	None

**Asymptomatic LVEF decrease*

These data confirm the results of the combination of Taxotere and Adriamycin , presented by Dieras [17], and compare also favorably with the published results of paclitaxel given over 3 hours infusion in combination with doxorubicin [19, 20] which has demonstrated a high incidence of CHF (20%).

2.5 Rationale for Going into the Phase III Adjuvant Setting

The adjuvant trials represent the ultimate setting for testing new and promising chemotherapy combinations and address the potential for cure. The subjectness of response rate assessment seen in metastatic trials is replaced by the objectiveness of outcome parameters (disease-free survival and ultimately overall survival). Any promising new combination must first prove its efficacy and favorable toxicity profile in the first line metastatic setting before testing in the adjuvant setting.

Taxotere is the leading compound of a new class of cancer agents called taxanes, which are confirmed as the most important entry in breast cancer therapy over the last two decades. They will be remembered in the future as being the drugs of the 1990's.

The results of Taxotere in monochemotherapy justify the development of combination chemotherapy. The most promising are based upon combinations of Taxotere and Adriamycin (TA) and Taxotere, Adriamycin and cyclophosphamide (TAC). These programs show a very high efficacy in first line treatment of metastatic breast cancer with response rates ranging from 85 to 90%.

Concomitantly, the toxicity profile is very favorable. The main toxicity is represented by a high incidence of neutropenia. However, neutropenia per se is no longer considered a clinically relevant concept and all clinicians agree that febrile neutropenia and sepsis are the occurrences to be followed particularly closely. In the case of TAC, the incidence of febrile neutropenia for patients with prophylactic antibiotics is 10.8% with no documented sepsis or toxic death. As well, the absence of clinical cardiac toxicity, significant peripheral edema and other major organ toxicities confirms the favorable tolerability profile of this combination and justify the swift move to the adjuvant setting.

One of the challenges to such a move was to design a trial with an acceptable control arm. The concept was to choose a standard chemotherapy usable by the majority of clinicians around the world. Although there is not one regimen standing out as the ultimate standard adjuvant protocol, an Adriamycin containing combination such as FAC, derived from the CALGB program, represents the best choice that is acceptable by international investigators.

The advantage is also that the randomized design of FAC versus TAC would compare 2 different regimens with the same doses of Adriamycin and cyclophosphamide in both arms. This reduces the risk of under or over use of one of these drugs in either of the arms. Simplicity of design with one appropriate question is the essence of good adjuvant trials.

The last problem was to choose the appropriate population for this trial. The node positive population was represents a high enough risk group to justify this type of program.

These reasons represent the rationale for using TAC as the experimental arm and FAC as the control arm in this study of the adjuvant treatment of women with operable breast cancer with involved axillary nodes.

III STUDY OBJECTIVES

Primary:

To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) in operable breast cancer patients with positive axillary lymph nodes.

Secondary:

To compare overall survival between the 2 above mentioned arms.

To compare toxicity and quality of life between the 2 above mentioned arms (appendix 9).

To evaluate pathologic and molecular markers for predicting efficacy (appendix 10).

An independent socio-economic study will be conducted in parallel with the clinical study.

IV PATIENT DEFINITION

4.1 Number of Patients/Enrollment Period/Follow-up Period

This is a multicenter, international study involving 1491 patients (745 TAC / 746 FAC). Enrollment started in June 1997 and stopped in June 1999 with a follow-up period of 10 years.

Interim analyses were performed in October 2001 and September 2003. Final analysis is planned when 590 DFS events will occur. A DFS/OS update is planned when 700 DFS events will occur.

4.2 Duration of Treatment

All included patients in both arms will receive a fixed number of 6 cycles of treatment.

TAC: 6 cycles

FAC: 6 cycles

4.3 Inclusion Criteria

1 Written or witnessed oral informed consent prior to beginning 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.

2 Histologically proven breast cancer. Interval between definitive surgery that includes axillary lymph node dissection and registration is less than 60 days.

3 Definitive surgical treatment must be either mastectomy, or breast conserving surgery **with** axillary lymph node dissection for operable breast cancer (T1-3, Clinical 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.

4 Histologic examination of the tumor: Invasive adenocarcinoma with at least one axillary lymph node (pN1) showing evidence of tumor among a minimum of six resected lymph nodes. At least one paraffin block from the primary tumor and nodes submitted to the central operational office ([redacted], Canada) for post-randomization confirmation of diagnosis and molecular studies (see Appendix 10).

5 Estrogen and progesterone receptors performed on the primary tumor prior to randomization. Results must be known by the end of chemotherapy in order to decide whether hormonal therapy is indicated.

6 Age ≥ 18 years and age ≤ 70 years. The upper age limit is not meant to be exclusionary but rather is based on the lack of safety data for the TAC regimen for women > 70 years of age.

7 Karnofsky Performance status index ≥ 80%.

8 Normal cardiac function must be confirmed by assessment of LVEF or shortening fraction (MUGA scan or echocardiography respectively). The result must be above the lower limit of normal for the institution.

9 Laboratory requirements: (within 14 days prior to registration)

a) Hematology:
   i) Neutrophils ≥ 2.0 10^9/L
   ii) Platelets ≥ 100 10^9/L
   iii) Hemoglobin ≥ 10 g/dL

b) Hepatic function:
   i) Total bilirubin ≤ 1 UNL
   ii) ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 UNL
   iii) Alkaline phosphatase ≤ 5 UNL
   iv) Patients with ASAT and/or ALAT > 1.5 x UNL **associated** with alkaline phosphatase > 2.5 x UNL are not eligible for the study.

c) Renal function:
   i) Creatinine ≤ 175 µmol/L (2 mg/dL);
   ii) If limit values, the calculated creatinine clearance should be ≥ 60 mL/min.

10 Complete staging work-up within 3 months prior to registration. All patients will have bilateral mammography, chest X-ray (PA and lateral), abdominal ultrasound and/or CT scan, and bone scan. **In case of positive bone scan, bone X-ray is mandatory to rule out the possibility of metastatic hot spots**. Other tests may be performed as clinically indicated (see appendix 5).

11 Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating center, which could be the Principal or Co-investigator's site.

12 Negative pregnancy test (urine or serum) within 7 days prior to registration for all women of childbearing potential.

4.4 Exclusion Criteria

1 Prior systemic anticancer therapy for breast cancer (immunotherapy, hormonotherapy, chemotherapy).

2 Prior anthracycline therapy or taxoids (paclitaxel, docetaxel) for any malignancy.

3 Prior radiation therapy for breast cancer.

4 Bilateral invasive breast cancer.

5 Pregnant, or lactating patients. Patients of childbearing potential must implement adequate non-hormonal contraceptive measures during study treatment (chemotherapy and tamoxifen therapy) and must have negative urine or serum pregnancy test within 7 days prior to registration.

6 Any T4 or N2 or known N3 or M1 breast cancer.

7 Pre-existing motor or sensory neurotoxicity of a severity ≥ grade 2 by NCI criteria.

8 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

9 Past or current history of neoplasm other than breast carcinoma, except for:
   a) curatively treated non-melanoma skin cancer
   b) in situ carcinoma of the cervix
   c) other cancer curatively treated and with no evidence of disease for at least 10 years
   d) ipsilateral ductal carcinoma in-situ (DCIS) of the breast
   e) lobular carcinoma in-situ (LCIS) of the breast

10 Chronic treatment with corticosteroids **unless** initiated > 6 months prior to study entry **and** at low dose (≤ 20 mg methylprednisolone or equivalent).

11 Concurrent treatment with ovarian hormonal replacement therapy. Prior treatment should be stopped before study entry.

12 Definite contraindications for the use of corticosteroids.

13 Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry.

14 Concurrent treatment with any other anti-cancer therapy.

15 Male patients.

V PLAN OF THE STUDY

This is a prospective, *non-blinded, randomized*, phase III trial. Patients will be post surgically stratified at inclusion into 2 groups according to the number of axillary lymph nodes involved (1 to 3; 4 and more) and will be randomly assigned to receive either:

- **TAC**: Docetaxel 75 mg/m² as 1 hour i.v. infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an i.v. bolus and cyclophosphamide 500 mg/m^2 as i.v. bolus on day 1 every 3 weeks (see 5.1.1 for administration schedule).

- **FAC**: 5-fluorouracil 500 mg/m^2 as an i.v. bolus on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an i.v. bolus and cyclophosphamide 500 mg/m² as an i.v. bolus on day 1 every 3 weeks (see 5.1.2 for administration schedule).

The chemotherapy doses will be calculated according to baseline body surface area(BSA) for all cycles. If there is a 10% or greater decrease in body weight compared to baseline, the BSA will be recalculated.

If the calculated BSA of the patient is > 2.2 m², the dose to be given to the patient will be calculated according to BSA = 2.2 m². No ideal body weight should be used for the calculation of BSA.

Dose reduction and/or treatment delay and treatment discontinuation are planned for the 2 arms in case of severe hematological and/or non-hematological toxicities.

- **Both Arms**: Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there is a contraindication for the use of tamoxifen therapy.

- **Both Arms**: Patients treated with lumpectomy will undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, may be used at the discretion of the treating radiation oncologist. This will be done in a consistent manner according to the guidelines at each institution.

No more than 8 days should elapse between the date of randomization and the start date of the first cycle of adjuvant chemotherapy.

5.1 Study Treatment

5.1.1 TAC Docetaxel in Combination with Doxorubicin and Cyclophosphamide

Doxorubicin will be given first
Dose: 50 mg/m², day 1
Route: 15 minute intravenous bolus
Schedule: every 3 weeks

followed by
Cyclophosphamide

Dose: 500 mg/m², day 1
Route: 1 to 5 minute intravenous bolus
Schedule: every 3 weeks

There will be a one-hour interval between the end of i.v. bolus of doxorubicin and the beginning of infusion of docetaxel.

Docetaxel

Dose: 75 mg/m², day 1
Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule: every 3 weeks

This is called *a cycle of treatment*. (for administration to patients see section 10.1.2).

Please note that if the treatment cannot be given within the timeframe accepted in the protocol (see section 5.2), the patient should however be treated with the treatment assigned during randomization unless clinically contraindicated.

5.1.2 FAC 5-fluorouracil in Combination with Doxorubicin and Cyclophosphamide

Doxorubicin will be given first

Dose: 50 mg/m², day 1
Route: 15 minute intravenous bolus injection
Schedule: every 3 weeks

followed by

5-fluorouracil

Dose: 500 mg/m², day 1
Route: 15 minute intravenous bolus injection
Schedule: every 3 weeks

and

Cyclophosphamide

Dose: 500 mg/m², day 1
Route: 1 to 5 minutes intravenous bolus injection
Schedule: every 3 weeks

This is called *a cycle of treatment*. (for administration to patients see section 10.1.2).

Please note that if the treatment cannot be given within the timeframe accepted in the protocol (see section 5.2), the patient should however be treated with the treatment assigned during randomization unless clinically contraindicated.

5.1.3 Post Chemotherapy Treatment

- **Both Arms**: Tamoxifen 20 mg p.o. daily for 5 years, starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors unless there is a contraindication for the use of tamoxifen therapy.

- **Both Arms**: Patients treated with lumpectomy will undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effect. Postmastectomy radiation therapy, and ipsilateral nodal radiation therapy, may be used at the discretion of the treating radiation oncologist. This will be done in a consistent manner according to the guidelines at each institution.

5.1.4 Prophylactic Antibiotic Therapy

Prophylactic antibiotic therapy **must** be administered to patients treated with docetaxel (TAC).

Ciprofloxacin is recommended at 500 mg p.o. b.i.d. for 10 days starting day 5 of each cycle.

Patients on FAC will use prophylactic antibiotics and G-CSF for all cycles following an episode of febrile neutropenia or infection (see section 5.2.1).

If ciprofloxacin is not available or not tolerated, another oral antibiotic **must** be used. The choice of the antibiotic is at the discretion of the investigator.

5.1.5 Prophylactic Premedication Regimen for Fluid Retention

The following premedication regimen must be administered for all patients treated with docetaxel (TAC) only.

Dexamethasone 8 mg p.o. for total of 6 doses.

1. night before chemotherapy
2. immediately upon waking the morning of chemotherapy
3. one hour before infusion of docetaxel
    - *note that this corresponds with the completion of doxorubicin infusion*
4. night of chemotherapy
5. morning the day after chemotherapy
6. evening the day after chemotherapy

5.1.6 Recombinant Granulocyte Colony Stimulating Factor (G-CSF/ Granocyte®/ Neupogen®)

No primary prophylactic administration (from first cycle) is permitted.

Indications: *The use of G-CSF is permitted only:*

- As curative treatment in case of febrile neutropenia or infection.
- As prophylactic treatment in patients with a prior episode of febrile neutropenia in earlier cycle (see dose modification section 5.2.1).
- As treatment for delayed recovery of absolute neutrophil count at day 21 (see section 5.2.1).

Use in prophylaxis:

Granocyte®: 150 µg (19.2 MIU)/m²/day

OR

Neupogen ®: 5 µg/kg/day (one vial = 300 µg for Neupogen 30 ® or 480 µg for Neupogen 48 ®)

Route: subcutaneously
Schedule: 1) Starting on day 4 following chemotherapy G-CSF will be administered once daily until day 11.

Day 1 being the day of the infusion, day 4 means 72 h after the day of the infusion.

2) On day 11, a CBC with differential will be performed.

a) If the ANC $\geq 1.0 \times 10^9$ / L ,then injections will stop.

b) If the ANC $< 1.0 \times 10^9$ / L , then injections will continue to complete 10 days of therapy, day 13 included.

5.1.7 Anti-emetic Treatment

A prophylactic anti-emetic treatment is recommended in both arms. However, the type of treatment (metoclopramide, granisetron, etc.) is at the discretion of the investigator.

5.2 Dose Modification

Each patient should be scheduled to receive all cycles of treatment at the same dose calculated according to BSA:

TAC: 75 mg/m² for docetaxel, 50 mg/m² for doxorubicin and 500 mg/m² for cyclophosphamide

OR

FAC: 500 mg/m² for 5-fluorouracil, 50 mg/m² for doxorubicin and 500 mg/m² for cyclophosphamide

Dose reduction is planned for both arms in case of severe hematological and/or non-hematological toxicities.

Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI common criteria (see Appendix 3).

IF A PATIENT EXPERIENCES SEVERAL TOXICITIES AND THERE ARE CONFLICTING RECOMMENDATIONS, PLEASE FOLLOW THE MOST CONSERVATIVE DOSE ADJUSTMENT RECOMMENDED.

NOTE THAT THE DOSES WHICH HAVE BEEN REDUCED FOR TOXICITY MUST NOT BE RE-ESCALATED (except for liver function tests if improved to within ranges given).

5.2.1 Dose Reduction in Both Arms

a) Neutropenia and/or its complications

Fever should be graded using the NCI grading system. The temperature should be measured orally.
In case of grade 2 fever concomitant with grade 4 neutropenia, the following approach is recommended:

If the patient has either three oral temperature determinations > 38°C during a 24-h period or a single elevation > 38.5°C, a therapeutic intervention should proceed immediately.

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy if ANC< 0.5 X 10^9/L

In case of febrile neutropenia (grade 2 fever (temp. ≥ 38.1°C) with grade 4 neutropenia (ANC < 0.5) requiring i.v. antibiotics and/or hospitalization) the blood counts must be done every 2 days until recovery of ANC ≥ 0.5 or temperature < 38.1°C. This must be documented on the CRF form for Febrile Neutropenia.

Febrile Neutropenia or Documented infection

Adverse event	Action to be taken for subsequent cycles
• Febrile Neutropenia • Documented infection	1. The first episode of febrile neutropenia or documented infection will result in the addition of: • **TAC:** G-CSF to all subsequent cycles • **FAC:** G-CSF and oral ciprofloxacin to all subsequent cycles 2. **Both Arms:** If there is a second episode, the patient will remain on ciprofloxacin and G-CSF and additionally, during the subsequent cycles all chemotherapeutic drug doses will be reduced by 20%. No further dose reductions are planned.

BLOOD COUNTS ON DAY 21

Neutrophils (x 10^9/L)	Action to be taken
≥ 1.5	Treat on time
< 1.5	1. Consider addition of G-CSF. CBC should be repeated every other day till day 35 • Proceed with full dose chemotherapy as soon as ANC ≥ 1.5. • Consider use of G-CSF in remaining cycles. 2. If there is no recovery on day 35, (ANC < 1.5 x 10^9/L), the patient will go off chemotherapy.

b) Nausea and Vomiting

Prophylactic antiemetic regimen is recommended in both arms from the first cycle. However, the type of treatment is at the discretion of the investigator. This may include corticosteroids.

c) Diarrhea

No prophylactic treatment for diarrhea is recommended. However, in case of grade 2 to 3 diarrhea, the patient should receive medication with loperamide.

In case of diarrhea ≥ grade 3 , reduce the dose of docetaxel from 75 to 60 mg/m² (TAC) or 5-fluorouracil from 500 to 400 mg/m² (FAC). If despite dose reduction, diarrhea still occurs at grade ≥3, the patient will go off chemotherapy.

d) Stomatitis

In case of grade 3 stomatitis (and/or oesophagitis):

- **TAC**: docetaxel will be reduced from 75 to 60 mg/m². If despite dose reduction, stomatitis still occurs at grade ≥3, doxorubicin will be reduced from 50 to 40 mg/m². No further dose reduction is planned.
- **FAC**: 5-fluorouracil will be reduced from 500 to 400 mg/m². If despite dose reduction, stomatitis still occurs at grade ≥3, doxorubicin will be reduced from 50 to 40 mg/m². No further dose reduction is planned.

e) Other toxic effects

Other toxic effects should be managed symptomatically if possible.

- For grade 3 toxicities except anemia (see appendix 3), in general drug should be held for a maximum of two weeks from the planned date of reinfusion until resolution to ≤ grade 1, then reinstituted, if medically appropriate. A dose reduction will be discussed between the investigator and sponsor.
- If grade 4 toxicity occurs, except anemia, the patient will go off chemotherapy.

f) Bilirubin and impaired liver function tests

Since no data in patients with abnormal bilirubin level treated with lower dose of docetaxel are available, in the event that bilirubin levels are abnormal during the study, the next cycle will be delayed by a maximum of two weeks. If no recovery, the patient should be taken off chemotherapy.

Since no data in patients with impaired liver function tests treated with lower dose of docetaxel are available, the same guidelines as for patients treated with higher dose of single agent docetaxel (100 mg/m²) will apply for this study.

In the event that ASAT and/or ALAT and/or alkaline phosphatase levels are abnormal in the absence of relapse, the following dose modifications should apply:

ASAT / ALAT values and Alkaline phosphatase values		**Dose modification**
≤ 1.5 x UNL	≤ 5 x UNL	no dose modification
> 1.5 x UNL to ≤2.5 x UNL	≤ 2.5 x UNL	no dose modification
> 2.5 x UNL to ≤5 x UNL	≤ 2.5 x UNL	**TAC:** Reduce dose of docetaxel from 75 to 60 mg/m² **and** reduce doxorubicin from 50 to 40 mg/m² **FAC:** Reduce dose of doxorubicin from 50 to 40 mg/m²
> 1.5 x UNL to ≤ 5 x UNL	> 2.5 x UNL to ≤ 5 x UNL	**TAC:** Reduce dose of docetaxel from 75 to 60 mg/m² **and** reduce doxorubicin from 50 to 40 mg/m² **FAC:** Reduce dose of doxorubicin from 50 to 40 mg/m²
> 5 x UNL	> 5 x UNL	**Both Arms:** Dose delay by a maximum of 2 weeks. If then no recovery to the above figures, patient should go off chemotherapy.

Once the dose was reduced due to impaired liver function, no further dose reduction is recommended if no worsening of the parameters is observed.

In case of recovery of liver function tests on the following cycle, the dose should be re-escalated to the previous dose-level.

5.2.2 Dose Modification Only in TAC

a) Peripheral neuropathy (see appendix 3, neurosensory and neuromotor)

In case of symptoms or signs experienced by the patient, dose modification should be performed as follows:

Grade 0,1: no change
Grade 2: TAC: retreat at dose reduced from 75 to 60 mg/m² for docetaxel (no further dose reduction is planned).
Grade 3: patient will go off chemotherapy

The same guideline applies also for patients with grade 1 neuropathy at baseline.

b) Cutaneous reactions (see appendix 3, skin)

Grade 0, 1, 2: No change
Grade 3: delay until ≤ grade 1, maximum two weeks then reduce dose of docetaxel from 75 to 60 mg/m² ; if no recovery to ≤ grade 1 within two weeks delay, patient will go off chemotherapy.

c) Anaphylactoid type reactions, hypersensitivity reactions

In the event that a hypersensitivity reaction occurs despite premedication, it is then very likely to occur within few minutes of start of the first or of the second infusion of docetaxel. Therefore, during the 1st and the 2nd infusions, the infusion must be given drop by drop for the first 5 minutes, and a careful evaluation of general sense of well being and whenever possible blood pressure and heart rate monitoring will be performed so that immediate intervention would occur in response to symptoms of an untoward reaction.

Facilities and equipment for resuscitation will be immediately available: antihistamine, corticosteroids, aminophylline, epinephrine.

If a reaction occurs, the specific treatment that can be medically indicated for a given symptom (e.g. epinephrine in case of anaphylactic shock, aminophylline in case of bronchospasm, etc.) will be instituted. In addition, it is recommended to take the measures listed below:

Mild symptoms: localized cutaneous reaction, such as: pruritus, flushing, rash	♦ Consider decreasing the rate of infusion until recovery of symptoms, stay at bedside. ♦ Then, complete docetaxel infusion at the initial planned rate. ♦ At subsequent cycles use the same premedication outlined in section 5.1.
Moderate symptoms: any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mm Hg	♦ Stop docetaxel infusion. ♦ Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent). ♦ Resume docetaxel infusion after recovery of symptoms. ♦ At subsequent cycles, give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one hour before infusion, in addition to the premedication planned in section 5.1.
Severe symptoms: such as bronchospasm, generalized urticaria, hypotension with systolic BP ≤ 80 mm Hg, angioedema	♦ Stop docetaxel infusion. ♦ Give i.v. dexamethasone 10 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent), add epinephrine as needed. ♦ Whenever possible resume docetaxel infusion within 3 hours after recovery or reinfuse the patient within 72 hours using i.v. dexamethasone 20 mg (or equivalent) and i.v. diphenhydramine 50 mg (or equivalent) one hour prior to resumption of infusion. ♦ At the subsequent cycles, dexamethasone (or equivalent) will be given at 20 mg orally the evening before chemotherapy, the morning of chemotherapy and one hour before docetaxel infusion. Additionally diphenhydramine (or equivalent) will be given at 50 mg i.v. 1 hour before docetaxel infusion. ♦ If a severe reaction recurs, patient will go off chemotherapy.
Anaphylaxis (NCI grade 4 reaction)	NO FURTHER STUDY DRUG THERAPY

d) Fluid retention (peripheral edemas and/or effusions)

In case fluid retention occurs during the treatment with docetaxel, the signs and symptoms should be graded as mild or moderate or severe as recommended in appendix 4.
NO DOSE REDUCTION IS PLANNED.
The weight will be recorded and followed as frequently as possible to document any weight gain which could be related to edema.

Recommended curative treatment for fluid retention

Curative treatment should commence when signs and/or symptoms of fluid retention are observed, including weight gain from baseline ≥ grade 1 not otherwise explained.
The following treatment is recommended in case fluid retention occurs:

- Furosemide 20 mg p.o. o.d.

If the symptoms cannot be controlled adequately, i.e. worsening of the fluid retention or spread to another area, the dose of furosemide should be increased to 40 mg. The addition of metolazone p.o. at the recommended dose together with potassium ± magnesium supplement may be useful.

The clinical tolerance of the patient and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or to discontinue the study drug. It is recommended, however, that patients with fluid retention of grade 3 severity (appendix 4) should be withdrawn from chemotherapy.

In case of difficulty to make a judgment whether an effusion would be disease related or study drug related, the treatment should be continued until progressive disease in other organs is documented.

Nail changes will not motivate dose-modification.

5.3 Guidelines for the Management of the Specific Toxicities (no dose modification required)

Cardiotoxicity of doxorubicin

Baseline measurements of LVEF or shortening fraction will be performed by either MUGA or echocardiography. No further routine assessments of LVEF are planned. Further assessments of LVEF at completion of chemotherapy or during the follow-up will be done at the discretion of the investigator.

Clinical symptoms and signs suggesting congestive heart failure (shortness of breath, tachycardia, cough, neck vein distention, cardiomegaly, hepatomegaly, etc.) must be investigated. LVEF should be determined by the same method used at baseline.

The patient should go off chemotherapy in case of congestive heart failure, or functional criteria for cardiotoxicity, or confirmation of decrease of LVEF according to Schwartz criteria (< lower limit of normal for institution and greater than 10% change).

Before considering the patient off treatment, LVEF should be repeated 4 to 7 days afterwards to confirm the decrease.

Patients who develop an LVEF decrease during the study will have repeated LVEF during the follow-up every 6 months for the first year and every year until the end of follow-up or otherwise as clinically indicated.

Extravasation:

No severe extravasation reactions have been observed so far with cyclophosphamide or docetaxel, however doxorubicin is a known chemical vesicant. As a general recommendation, in the event of extravasation, the following advice should be observed for patients treated in both arms.

1. Stop the infusion immediately.
2. Do not remove the needle or cannula.
3. Aspirate with the same needle as much infiltrated drug as possible from the subcutaneous site.
4. Apply ice to area for 15 to 20 minutes every 4 to 6 hours for the first 72 hours.
5. Paint the skin over the extravasated site with 100% DMSO 4 times daily for 2 weeks (or hyaluronidase).
6. Watch the area closely during the following days in order to determine whether a surgical excision and skin graft is necessary.

5.4 Radiation Therapy

Treatment will begin 3 to 8 weeks after the chemotherapy is completed.

Radiation therapy will be indicated according to the guidelines of each institution.

Advised indications are as follows:

Radiotherapy will be mandatory in case of breast conserving surgery. It will be allowed, but not mandatory, in case of mastectomy, according to the policy in use at each participating center. If radiotherapy is indicated, the center will follow the policy in use in the institution and will provide a copy of this policy to the BCIRG. Boost radiation therapy will be left at the discretion of the investigator.

5.5 Treatment Duration and Follow-up

Both regimens should be administered for a maximum of 6 cycles. In the event of relapse or unacceptable toxicities, treatment should finish earlier.

Therapy after protocol treatment is discontinued

If patients are removed from therapy because of disease progression, further treatment is at the discretion of the investigator.

Except hormonotherapy and radiotherapy as per protocol, no further anti-tumor therapy is allowed (e.g. surgery, chemotherapy, immunotherapy, etc.) after completion of the chemotherapy and before breast cancer relapse or second primary malignancy is documented. If this is not possible, such anti-cancer therapy will be considered as a protocol violation but will not impact the efficacy analyses. The use of Aromatase Inhibitors in post-menopausal subjects will not be considered as a major protocol violation. When considered in the treatment of postmenopausal subjects (according to each institution's guidelines), the use of Aromatase Inhibitors must be accurately documented and reported on the CRF (page FU4).

Follow-up after study

Patients will be observed during one month after last study drug infusion until end of study to document outcome of ongoing side effects (see section IX). Clinical adverse experiences requiring further ongoing evaluation include:

- ongoing clinical adverse experiences possibly or probably related to study drug at the time of End of Chemotherapy.
- relevant non cancer related signs and symptoms occuring after completion of chemotherapy (i.e. congestive heart failure, toxicities related to Tamoxifen and/or radiotherapy...).
- acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) occurring after completion of chemotherapy.

Patients will also be followed every 6 months for the first five years and then once a year for ten years or until relapse to document:

- Disease-free survival
- Survival
- Further therapy
- Quality of life (for the first two years only)
- Late side effects

5.6 Concomitant Treatments

Allowed:
1 G-CSF (in case of febrile neutropenia or infection or delayed neutrophil counts) (see sections 5.1.6 and 5.2.1)
2 Antiemetics (section 5.1.7)
3 Antiallergic measures (section 5.2.2)
4 Antibiotics
    - oral prophylactic
    - i.v. curative in case of febrile neutropenia or documented infection.

Ancillary treatments will be given as medically indicated. They must be specified in the Case Report Form.

Not permitted:

1 The patients will not receive other investigational drugs and anticancer treatment while on study (till relapse or up to 10 years).
2 Corticosteroids are not allowed, except as outlined in section 5.1.5 (premedication), sections 5.2.1 b) and 5.1.7 (antiemetic), and section 5.2.2 c) (acute hypersensitivity reaction).
3 Concomitant treatment with bisphosphonates will not be allowed during the course of active treatment with chemotherapy. Subsequently, bisphosphonates may be used only for non-oncologic indications.
1. Concomitant treatment with amifostine (Ethyol®) will not be allowed during the course of active treatment with chemotherapy.
2. Concomitant treatment with Cardioprotectors (e.g. Dextrazoxane®) will not be allowed during the course of active treatment with chemotherapy.

5.7 Prestudy Screen

	INVESTIGATIONS	TIMING within (time) prior to registration
1 Patient informed consent	Obtained	**Before study entry**
2 History and physical exam	**History** - including: diagnosis of breast adenocarcinoma, prior antitumor therapy and outcome, menopausal status, receptor status at diagnosis, general medical history including cardiac history and allergy, concurrent illness. Concomitant medications, and their indication, used within one month prior to study entry. **Physical Exam** - including: height and weight, Karnofsky index for performance status.	14 days
3 Hematology *	hemoglobin WBC and neutrophil count platelets count	14 days
4 Biochemistry *	**Liver function:** • Alkaline phosphatase, • ASAT (SGOT), ALAT (SGPT), • bilirubin **Renal function:** • serum creatinine, • creatinine clearance (if indicated)	14 days Liver function tests are to be repeated within 3 days, if abnormal results.
5 Pregnancy test	urine or serum (if applicable)	7 days
6 Imaging	**mandatory for all patients:** • bilateral mammography • chest-X-Ray (PA and lateral) • abdominal ultrasound and/or CT scan • bone scan and bone X-ray in case of hot spots in bone scan Other instrumental examinations as indicated.	3 months
7 ECG	ECG	3 months
8 LVEF	MUGA scan or echocardiography	3 months
9 Quality of life	QLQ - C30 and BR23 questionnaires (see appendix 9)	14 days
10 Other Investigations	as clinically indicated	3 months
11 Existing signs and symptoms	Baseline evaluation to document existing symptoms.	14 days

* Laboratory assessments will be performed whenever possible by the same laboratory throughout the study.
** To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ ultrasounds/ must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner).
Every effort will be made to use the same instrumental examination from baseline through follow-up.

5.8 Study Entry - Registration

All eligible patients must be registered with the Breast Cancer International Research Group study Data Manager [redacted] (Canada) prior to start of treatment.
A patient who has not been registered before the first treatment administration will not be accepted for the study at a later date.

The registration forms should be faxed to B.C.I.R.G.-Registration officer [redacted] (Canada):

[redacted]

Registration can be made once eligibility of the patient is checked (including laboratory and radiological results).

The following information will be requested:

1 Protocol number
2 Institution name
3 Caller's name
4 Investigator's name
5 Patient's identification **(first two letters of first name and first letter of surname)**
6 Patient's chart number (optional)
7 Patient's birth date (day/month/year)
8 Performance status
9 Date treatment planned.
10 Verification of all inclusion and exclusion criteria with values of hematologic and biochemical assessments, radiological results and dates of all examination performed.

Each eligible patient will be randomized according to a center specific randomization block to receive either docetaxel, doxorubicin and cyclophosphamide (TAC) or 5-fluorouracil, doxorubicin plus cyclophosphamide (FAC).

The Registration Officer will notify the investigator by fax, within 2 working days, with the patient's study number and the randomly allocated treatment group.

5.9 Evaluation During Chemotherapy

All patients during the study must be evaluated according to the schedule outlined in Appendix 5 until they come off chemotherapy.

Schema during chemotherapy

	INVESTIGATIONS	TIMING
1 History and physical Exam	**Clinical History since previous infusion** **Physical Exam -** including: Weight, Karnofsky index for performance status Clinical tumor assessment	every 3 weeks (day 1 or day -1 of each cycle before chemotherapy)
2 Hematology	Hemoglobin, WBC, neutrophils, and platelets count.	every 3 weeks (day 1 or day -1 of each cycle before chemotherapy)
3 Biochemistry	Alkaline phosphatase, ASAT (SGOT), ALAT (SGPT), bilirubin, serum creatinine, creatinine clearance (if indicated)	every 3 weeks (within 3 days prior to chemotherapy)
4 ECG		as clinically indicated
5 LVEF	MUGA or echocardiography	as clinically indicated
6 Quality of life	QLQ C30 and QLQ BR23 questionnaires	day -1 or day 1 C3 and C5 (before chemotherapy)
7 Other Investigations		as clinically indicated
8 Adverse events(**)	Investigations as indicated	Serious Adverse Events should be reported within 24 hours anytime
(**) Toxicities will be recorded and graded according to the NCI - CTC criteria (Appendix 3). In case NCI-CTC criteria are not applicable the event should be defined as 1 = mild, 2 = moderate, 3 = severe and 4 = life-threatening.		
Laboratory assessments will be performed whenever possible by the same laboratory throughout the study. To ensure comparability, the baseline X-rays/ultrasounds/scans and subsequent X-rays/ ultrasounds/ scans must be performed using identical techniques (i.e., scans performed immediately following bolus contrast administration using a standard volume of contrast, the identical contrast agent, and preferably the same scanner). **Every effort will be made to use the instrumental examination from baseline through follow-up.**		

5.10 Evaluation at End of Chemotherapy

To be performed 3-4 weeks after the last treatment as summarized in Appendix 5: work-up will include = **physical examination, hematology, biochemistry, record of toxicity, and quality of life**.

5.11 Follow-up After End of Chemotherapy

Follow-up visits will be every 6 months for the first five years, then once a year for 10 years. Clinical follow-up may be more frequent according to the standard of practice at the participating center.

First 2 years	every 3 months	physical examination
	every 6 months	hematology and biochemistry in addition to physical examination
	every 12 months	mammography and chest X-ray in addition to physical examination, hematology and biochemistry
Years 3 to 5	every 6 months	physical examination, hematology, biochemistry
	every 12 months	mammography and chest X-ray in addition to physical examination, hematology, biochemistry
Years 6 to 10	every 12 months	physical examination, hematology, biochemistry, Mammography, **LVEF assessment (MUGA scan or echocardiography)**

Other diagnostic tests (i.e.: abdominal ultrasound and/or CT scan, bone scan) should be performed only in presence of signs and/or symptoms suggestive of cancer recurrence.

Quality of Life assessment is required 6 months, 12 months and 24 months after End of Chemotherapy.

Clinical adverse experiences requiring further ongoing evaluation include:

- ongoing clinical adverse experiences possibly or probably related to study drug at the time of End of Chemotherapy.
- relevant non cancer related signs and symptoms occuring after completion of chemotherapy (i.e. congestive heart failure, toxicities related to Tamoxifen and/or radiotherapy...).
- acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) occurring after completion of chemotherapy.

5.12 Dropouts

The reason and date of chemotherapy discontinuation for all patients will be documented on the case report form (e.g. completed study, adverse event, lost to follow-up, etc.).

The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from the study.

VI SAFETY AND EFFICACY PARAMETERS (see Appendix 5)

6.1 Safety Evaluations

6.1.1 Clinical Safety

The following tests will be performed prior to and/or on specified days during and following therapy:

- Complete history of malignant and non-malignant diseases including known hypersensitivity reactions and cardiac history.
- Full clinical examination, vital signs (blood pressure, heart rate, temperature), height, weight, assessment of any residual toxicity due to previous therapy, assessment of performance status according to Karnofsky Index.
- Electrocardiogram (ECG), left ventricular ejection fraction (LVEF)
- Chest X-ray
- Adverse events: each patient will be assessed regularly for potential adverse events according to the NCI (Appendix 3).

Toxicities which cannot be graded using the NCI common toxicity criteria will be graded as followed:
- mild (asymptomatic)
- moderate (symptomatic but not interfering significantly with function)
- severe (causing significant interference with function)
- life threatening

6.1.2 Laboratory Determinations

The following tests will be performed prior to and on specified days during and following therapy:

- Hematology: WBC, neutrophils and platelets count, hemoglobin
- Biochemistry: total bilirubin, alkaline phosphatase, SGOT (ASAT), SGPT (ALAT) creatinine, creatinine clearance (as indicated)
- Pregnancy test: urine or serum (if applicable)

6.2 Efficacy Evaluations

All randomized patients will be included in an intention to treat analysis.

If one study chemotherapy drug is discontinued (whatever the reason), the patient will be analysed in the Disease Free Survival and Survival analysis according to the intent-to-treat analysis.

6.2.1 Objective Relapse

Any clinical or radiologic evidence of tumor relapse including the central nervous system. Obtain histology or cytological proof of failure, if feasible. Detail on flow sheets the appearance of any evidence of malignant disease. Follow for survival.

6.2.1.1 Local relapse

Defined as evidence of tumor in the breast surgical scar, ipsilateral breast (conservative surgery), or evidence of tumor in the ipsilateral anterior chest wall (mastectomy) or skin or soft tissues within the local area.

Histologic or cytologic proof is preferred.

6.2.1.2 Regional relapse

Defined as evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, and infraclavicular) as well as skin or soft tissues within the regional area.

Histologic or cytologic proof is preferred.

6.2.1.3 Distant relapse

Defined as evidence of tumor beyond the local-regional level as previously defined.

This includes the following:

1) lymph nodes not included in the areas defined above
   (i.e. supraclavicular, contralateral axilla, paratracheal, etc.)
2) skin not included in the areas defined above
3) liver
4) lung
5) bone
6) central nervous system
7) contralateral breast
8) other sites not defined above

Histologic or cytologic proof is preferred especially in solitary lesions.

Positive bone scans must be correlated with bone X-ray.

Multiple pulmonary nodules on chest X-ray, multiple liver nodules on liver ultrasound or CT-scan, multiple lytic or blastic bone lesions or multiple hot spots on the bone scan will be acceptable without pathologic correlation.

Any new breast malignancy must be biopsied if possible and blocks must be sent to the central operational office ([redacted], Canada) for confirmation of primary or metastatic status along with pathologic and molecular studies.

6.2.1.4 Other circumstances

The following do not constitute progression, however, they should initiate a new evaluation for extent of disease:

10% or more decrease in baseline Karnofsky performance status

A single new lesion on bone scan without evidence of lytic disease by radiography or bone scan.

Elevation of serum markers such as CEA or CA15-3 by themselves will not constitute evidence of relapse without other objective evidence of relapse. These studies are not recommended.

6.2.2 Second Primary Cancer

Defined as any other histopathologically proven cancer including second invasive primary breast cancer in ipsilateral or contralateral breast. Excluded are non-melanoma skin cancer, in-situ carcinoma of the cervix, and in-situ carcinoma of the breast (LCIS/DCIS).

6.2.3 Disease-Free Survival

Disease-Free Survival (DFS) will be calculated from the date of randomization up to the first date of local, regional, or distant relapse, second primary cancer, or death.

6.2.4 Survival

Survival will be measured from the date of randomization up to the date of death of any cause.

VII QUALITY OF LIFE EVALUATION (see Appendix 9)

The EORTC quality of life instruments were chosen in this comparative study.

The QLQ-C30 profile questionnaire and QLQ-BR23 module specific to breast cancer are, respectively, 30 and 23 items in a questionnaire format. They will be self administered by the patient (see appendix 9) and should be completed within 7 days before randomization, then after every 2 cycles of chemotherapy (day -1 or day 1 of 3rd and 5th course), then at end of chemotherapy visit (3 to 4 weeks after last chemotherapy cycle), and subsequently at 6, 12 and 24 month follow-up visits (total of 7 administrations).

The patient should complete the questionnaire at the center just prior to treatment.

It is recommended that a key person (e.g. research nurse) at each center should be responsible for questionnaire data collection in order to optimize the compliance of the patient and to ensure the completeness of the data.

VIII DATA ANALYSIS / STATISTICAL CONSIDERATIONS

8.1 Efficacy evaluation

8.1.1 Efficacy Parameters

Primary

The primary evaluation of efficacy will be the comparison of the Disease-Free Survival (DFS) between the two treatment groups after 590 events are observed overall. The DFS is 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. Additionally the comparison of the Overall Survival (OS) between the two treatment groups will be performed.

Secondary

Secondary criteria will consist of the comparison of the two treatment groups based upon quality of life and on the pathologic and molecular markers for predicting efficacy (Appendix 10).

8.1.2 Overall Strategy

The primary objective of the study is to compare treatment groups both overall and in the subgroup of patients with one to three positive axillary nodes for Disease Free Survival after 590 events are observed overall.

The current sample size calculation will allow for the following strategy of analysis [32]:

- Step 1:

to perform an overall comparison of treatment groups stratified for the nodal status (at a 5% significance level).

- Step 2:

In case of non-significant difference at step 1, no statistical comparison of treatment groups will be performed within subgroup.

In case of significant difference at step 1, to perform statistical tests by subgroup in patients with one to three (namely « stratum 1-3 » hereafter) and with four or more (namely « stratum 4+ » hereafter) positive axillary nodes respectively (at a 5% significance level).

- Step 3:

In case of an overall significant difference (step 1) and a significant difference in only one of the 2 subgroups (step 2), to perform an interaction test between the nodal status and the treatment (at a 15% significance level).

If the interaction test is not statistically significant, the conclusion will be that there is no objective reason to state that the observed treatment effect is different between strata. The effect within each stratum will be actually the one observed overall.

If the interaction test is statistically significant, the conclusion will be that the treatment effect is limited to the stratum where the subgroup analysis led to a significant p-value.

8.1.3 Sample Size Determination

The study will have sufficient power to compare TAC and FAC for all patients randomized with stratification by nodal status as well as for the separate strata for patients with one to three positive axillary nodes and patients with 4+ positive axillary nodes. The planned sample size per treatment group is 708 patients with 495 in the 1-3 stratum and 213 in the 4+ stratum.

[redacted]

As specified in section 8.1.2, the comparison of TAC and FAC for all randomized patients will be made first (in step 1) of the primary objective of this study. [redacted]

Thus, the role of the interaction test in step 3 of Section 8.1.2 is reasonable relative to the evaluation of whether the treatment effect is limited to the 1-3 stratum when it is the only stratum which provides a significant result. It is considered similarly reasonable for other situation with interaction such as those for which 4+ stratum only has a significance.

The second interim analysis performed in September 2003, with a median follow-up of 55 months, has already demonstrated a statistical significant benefit in DFS and OS in favor of TAC, overall and in the 1-3 positive node group. [redacted]

8.1.4 Statistical Methodology

8.1.4.1 Populations to be Analyzed

The primary efficacy analysis will be performed on the **Intention-to-Treat (I.T.T.) population**, defined as the population of all randomized patients analyzed in the treatment group they were assigned to. Randomized patients who did not receive chemotherapy will be analyzed in their group of randomization. The ITT analysis will be performed for the DFS and for the overall survival. In addition, the analysis of DFS will be performed on the **eligible patients population**.

The safety analysis will be conducted on all patients who started at least one infusion of the study treatment.

8.1.4.2 Statistical Methods

The Kaplan-Meier product limit method will be used to estimate the DFS and the OS and the logrank test will be used to compare the two treatment groups for both the DFS and OS. All tests of hypotheses will be two-sided. Confidence intervals of the median survival will be calculated using the Simon method [24].

In addition, Cox's multiple regression analysis will be performed for DFS and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include the number of axillary lymph nodes involved, age, menopausal status (seedefinition in appendix 12), type of surgery, histopathological findings, ER/PR status, tumor size and pathological markers (see Appendix 10). The covariates which appear unbalanced at baseline will conceivably be added in the Cox model.

In the statistical analysis, a center will correspond to a participating institution. It is expected to have at the end of the study a large number of centers with few patients per center. It is consequently not planned to include any center effect in the statistical model.

However, if there is a large difference of recruitment in some centers, it is planned to compare the consistency of the results between this (these) large center(s) and the entire study results, in terms of major baseline characteristics and primary endpoint.

8.1.4.3 Interim Analysis and Follow-up Analyses

One interim efficacy analysis will be performed 3 years after recruitment of 50% of the expected patients (708 patients).The group sequential design, according to Peto's method [25], will be used at a significance level of 0.001 for the interim analysis. This allows the use of an unadjusted level of 0.05 for the final analysis. At the time of the interim analysis, all patients should have been recruited. Except in the case of overwhelming interim results, the recommendation to use FAC or TAC in the target patients population will be given after the final analysis (5-year analysis) at the discretion of the Steering Committee.

Further to the 3-year interim efficacy analysis conducted in October 2001, the IDMC recommended an additional interim analysis to take place after observing a total of 400 first DFS events, with the treatment comparison to be performed at the 0.001 level.

Furthermore, a significant level of 0.048 will be used for the final analysis, as suggested by the FDA in order to protect the overall experiment-wise type I error at the 0.05 level.

Some patients are expected to have a very long disease free survival. Consequently, an efficacy (DFS, OS) and safety update will be conducted once 700 DFS events are observed, as per the FDA requirement.

8.2 Safety Evaluation

The National Cancer Institute Common Toxicity Criteria (NCI-CTC) and the corresponding grading system will be used to grade adverse events for recording in the CRF. For all adverse events not classified by the NCI-CTC a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, and 4 life threatening).

Adverse events will be compared using a two-tailed Cochran Mantel Haenszel test. In view of the anticipated large number of statistical tests, p-values will not be interpreted in the usual sense but will be used as a “flagging device” to highlight differences worth further attention.

8.3. Data monitoring Committee

In addition to the Steering Committee, a Data Monitoring Committee (DMC) will be set up. It will be composed of at least two oncologists and one statistician. These members will be independent of the trial and familiar with the methodology of oncology trials. They must be aware of the dangers of conclusions based on immature data and agree with the design and the goals of this protocol.

The mission of the DMC will be to ensure the ethical conduct of the trial and to protect the safety interests of patients in this study. This committee ensures the feasibility and progress of the trial.

In the absence of any major event requiring the meeting of the DMC members, an annual meeting of the DMC will be held. The first review of the trial by the DMC is forecasted for October 1998. The DMC will have written operating procedures and will maintain records of all its meetings.

Before any meeting of the DMC, the Data Center should provide the DMC with at least the following key documents:

- eligibility data
- on study protocol deviations (i.e. error in treatment allocation, early discontinuation of chemotherapy without any reason, unacceptable concomitant treatment, etc.)
- patient accrual
- lost to follow-up patients
- summary of patient and tumor characteristics
- summary of drug delivery
- toxicity data
- and any other major problems encountered.

All data will be broken down by treatment group and participating institution (if applicable). In addition, the Data Center will provide the DMC with efficacy data at the time of the interim analysis (3-year analysis). All results are confidential and must not be divulged to nonmembers of the Data Monitoring Committee. After each meeting, the DMC will give recommendations to the Steering Committee either to continue the trial unchanged, to modify the trial (with reasons), or to discontinue the trial (with reasons). The final decision to amend the protocol or to discontinue the trial will be taken only by the Steering Committee.

8.4. Review of the Statistical Analysis Plan

The above analysis plan will be reviewed before the end of recruitment of patients (blinded review). During this review, the management of irregularities will be determined and detailed in the final “statistical analysis plan”. This document will be submitted to the Data Monitoring Committee and the Steering Committee and will be filed in the Rhône-Poulenc Rorer central file.

IX ADVERSE EVENTS / TOXICITY

- When toxicity occurs, it should be graded according to the NCI (Appendix 3).

Definition of an adverse event

Patients will be instructed by the investigator to report the occurrence of any adverse event. *An adverse event is any undesirable event associated with the use of a drug, whether or not considered drug related, and includes any side effect, injury, toxicity, or sensitivity reactions. It also includes any undesirable clinical or laboratory change which does not commonly occur in the patient.*

- **Serious event**

A serious adverse event (SAE) is any event that is fatal, life-threatening, requires or prolongs hospitalization, results in persistent or significant disability or incapacity, a congenital anomaly or birth defect, an important medical event.
Important medical events are those which may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes. Cancer and drug overdosage or abuse will normally be considered as serious.

All serious adverse events occurring during the study treatment period (i.e. during TAC or FAC chemotherapy period) or within 30 days following the last infusion of chemotherapy must be reported according to the procedure described below. Any late SAE (occurring after this 30 day period) possibly or probably related to the study chemotherapy should follow the same reporting procedure.
As a convention for this study, congestive heart failure, acute myeloid leukemia and myelodysplastic syndrome will always be considered as a Protocol Defined Serious Adverse Event, during chemotherapy or follow-up period regardless of the relation to study drug(s).

Progression of a patient's underlying condition leading to one of the above should be reported as a serious (but expected) adverse experience which is (a) unrelated to the study drug, or (b) caused by failure of the anticipated therapeutic effect of the study drug.

"Life-threatening" means that the patient was at *immediate* risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

"Requires inpatient hospitalization" should be defined as hospital *admission* required for treatment of the adverse event. Hospital admission for scheduled elective surgery would not be a serious adverse event.

If the adverse event is serious, it must be reported *within 1 working day by telephone and/or fax* and in writing within 3 days to the following individuals using an Adverse Event Report Form (appendix 7):

B.C.I.R.G. Study Pharmacist:
[redacted]

Rhône-Poulenc Rorer National Affiliate Representative
See pages 4 to 7

The B.C.I.R.G. Study Pharmacist and the Rhône-Poulenc Rorer National Affiliate Representative will forward the SAE to Rhône-Poulenc Rorer Corporate Pharmacovigilance. The National Affiliate Representative will also send the report to local or national authorities in accordance with the investigating center's policies and Rhône-Poulenc Rorer Corporate Pharmacovigilance.

Rhône-Poulenc Rorer Corporate Pharmacovigilance will submit all queries if any to the B.C.I.R.G. Study Pharmacist.

All queries to the investigating center will be coordinated though the B.C.I.R.G. central office.

Withdrawal from the study and therapeutic measures shall be at the discretion of the investigator. A full explanation for the discontinuation from the study will be made on the appropriate case report form. All adverse events, regardless of severity, will be followed up by the investigator until satisfactory resolution; local authorities will be informed by the investigator according to local regulations.

Rhone-Poulenc Rorer (or its affiliate) has a legal responsibility to notify both the local and international regulatory authorities about the safety of a new drug. Prompt notification of major adverse events by the investigator is essential so that legal obligations are met.

The investigator and persons in charge of patient care should institute any supplementary investigations of major adverse events based on their clinical judgment of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the adverse event. Rhone-Poulenc Rorer may suggest special tests based on expert advice. If a patient dies, any post-mortem findings including histopathology must be provided to Rhone-Poulenc Rorer.

Withdrawal from the study and therapeutic measures shall be at the discretion of the investigator. A full explanation for the discontinuation from the study will be made on the appropriate case report form.

All other minor adverse reactions will be collected on the CRF during the study.

In agreeing to the provisions of this protocol, these responsibilities are accepted by the investigator.

Death on Study

Any death occurring during the active treatment part of the study and within 30 days following the last infusion must be reported to the B.C.I.R.G. and the Rhône-Poulenc Rorer national affiliate (see pages 4-6) within 24 hours, regardless of the relation to study drug(s). Deaths occurring during the study follow-up period, need only to be reported as serious adverse events if it is thought that there is a possible relation to the study drug(s). All deaths should be reported on the death report form section of the CRF regardless of cause.

The cause of death should be documented (cancer-related, treatment-related, cancer and treatment-unrelated). Autopsy reports should be collected whenever possible and sent to the central operational office in [redacted] (Canada).

X STUDY MEDICATION

Docetaxel and Lenograstim will be supplied by Rhône-Poulenc Rorer. Concerning doxorubicin, Adriamycin® (Pharmacia) should be used.

10.1 Drug Packaging, Labeling, Dispensing and Storage

10.1.1 Packaging and Labeling

Further to the change of study number from « 316A » to « 316 » (1st amendment dated September 19, 1997), drug supplies prepared prior to this date will bear the study number « 316A » while those prepared after will mention « 316 » as the study number.

Any batch numbered « 316A » will be used until expiry date and is likely to be stored until then.

A). DOCETAXEL (see Appendix 8 for detailed information)

Docetaxel will be provided as a sterile concentrate for infusion.
The appropriate solvent for diluting the docetaxel concentrate for infusion will also be provided.
Vials are intended for single administration only.

- The label affixed to each box of Taxotere® will contain the following information:

FOR CLINICAL TRIAL USE ONLY KEEP OUT OF THE REACH OF CHILDREN **RP 56976 - V - 316** ..... TAXOTERE® VIALS concentrate for infusion EACH VIAL : 80 mg/2mL (40 mg/mL) FILL 94.4 mg / 2.36 mL **CAUTION : DILUTION REQUIRED** **READ THE INSTRUCTIONS FOR USE IN THE PROTOCOL** Batch CB..... VR..... USE BEFORE$^{\Delta}$.....	KEEP IN REFRIGERATOR PROTECT FROM LIGHT Dilute each Taxotere® 80 mg vial with the entire contents of the corresponding solvent vial

Δ If it is a legal requirement

- Attached to each vial of Taxotere® will be a colored label containing the following information:

Fixed label	**Tear-off label**
RP 56976 - V - 316 TAXOTERE® vial concentrate for infusion 80 mg/2 mL (40 mg/mL) Fill : 94.4 mg/2.36 mL Dilution required Batch CB..... VR.....	**RP56976 - V-316** TAXOTERE® vial Patient's initials: ..... Date of Birth : ..... Date of infusion: ..... Batch CB..... VR.....

- Attached to each box of the solvent vial will be a label containing the following

FOR CLINICAL TRIAL USE ONLY
KEEP OUT OF THE REACH OF CHILDREN
RP 56976-V-316
..... Solvent vials
13% (w/w) ethanol in water for injection
Each vial Fill : 7.33 mL
Read the instructions for use in the protocol
Batch CB..... VR.....

USE BEFORE$^{\Delta}$.....

Dilute each Taxotere® 80 mg vial with the entire contents of the corresponding solvent vial

Δ If it is a legal requirement

- Attached to each vial of the solvent will be a white label containing the following information:

Fixed label	**Tear-off label**
RP 56976-V-316 SOLVENT VIAL 13% (w/w) ethanol in water for injection Fill : 7.33 mL TO DILUTE ONE TAXOTERE® 80 MG VIAL USE THE ENTIRE CONTENTS OF ONE SOLVENT VIAL Batch CB..... VR.....	**RP 56976-V-316** SOLVENT VIAL Patient's initials :..... Date of birth :..... Date of infusion:..... Batch CB..... VR.....

B) rHuG-CSF / LENOGRASTIM (GRANOCYTE®)

Where available, lenograstim will be provided as sterile vials of lyophilisate of white powder corresponding to 263µg of lenograstim per vial.
The solution must be reconstituted with one ml of water for injections

- Vials Labelling:

Rhone-Poulenc Rorer
For Clinical trial Use only
Keep out of the reach of Children
RP56976-V-316
GRANOCYTE®
Lenograstim 263 µg
For subcutaneous administration
Store between +2°C and +8°C
Batch.Nr .... VR.....
Chugai Rhone Poulenc

- Boxes :

Rhone-Poulenc Rorer
For Clinical trial Use only
Keep out of the reach of Children
RP56976-V-316
GRANOCYTE® Lenograstim 263µg
10 vials of Lenograstim 263µg
For subcutaneous administration
Each vial to be reconstituted with 1 ml water for injection prior to use
Store between +2°C and +8°C
Batch.Nr .... VR.....
Chugai Rhone Poulenc

- Water for injections :

Rhone-Poulenc Rorer
RP56976-V-316
x Ampules 1ml Water for injection
1 ml to be used to reconstitute a vial of Lenograstim 263µg
For subcutaneous administration
Batch.Nr .... VR.....
Chugai Rhone Poulenc

In countries where Granocyte® is not available, Neupogen® will not be supplied.

10.1.2 Administration to Patients

Handling precautions:

Drug handling precautions for cytostatic drugs should be followed. Avoid contact or inhalation.

10.1.2.1 Docetaxel (see Appendix 8)

For preparation of the docetaxel solution, please refer to Appendix 8.

The drug will be administered to the patient as a *one hour i.v. infusion*, Use of a peristaltic *infusion pump* is recommended. Doxetaxel should be given drop by drop for the first 5 minutes of the first 2 infusions to prevent AHSR.

10.1.2.2 Doxorubicin

See preparation instructions on the package insert.

10.1.2.3 Cyclophosphamide

See preparation instructions on the package insert.

10.1.2.4 5-Fluorouracil

See preparation instructions on the package insert.

10.1.3 Storage (see Appendix 8)

All drug supplies must be kept in an appropriate locked room which can be accessed only by the pharmacist, the investigator or a duly designated person.

The vials of docetaxel (Taxotere®) should be stored as specified in Appendix 8.

For the vials of doxorubicin (Adriamycin®), cyclophosphamide, 5-Fluorouracil: see storage instructions on the package insert

10.2 Drug Accountability

The person responsible for drug dispensing is required to maintain adequate records of all supplied study drugs. These records (e.g., drug movement form and tear-off labels from the medication vials: Taxotere®) include the dates the study medications are received from Rhone-Poulenc Rorer, dispensed for the patient and returned to Rhone-Poulenc Rorer.The labels of the vials (Taxotere®) administered to patients must be completed (patient's initials, date of birth, date of infusion) and sticked in the CRF.

The person responsible for drug administration to the patient will record precisely the date and the time the drug is administered to the patient. In case the drug infusion has to be stopped, the exact date and time that the infusion has been stopped and restarted will be carefully recorded.

XI ADMINISTRATIVE ASPECTS

11.1 Monitoring, Auditing, and Inspecting

The study will be monitored by regular site visits and telephone calls to the investigator by members of the B.C.I.R.G Clinical Research Department. During site visits, the monitor should review original patient records, drug accountability records and document retention. Additionally, the monitor should observe study procedures and will discuss any problems with the investigator. During the course of the study, the Clinical Quality Assurance Department of Rhône-Poulenc Rorer Research and Development may conduct an on-site audit visit. The investigator will provide direct access to source data/documents for trial related monitoring, audits, IRB/EC review and regulatory inspections.

11.2 Patient Identification

All patients screened for the study will have their initials and birth date entered chronologically on the patient log at the initial visit. In the event a patient is excluded from study participation, the reason is to be documented in the space provided on the patient log.

Each patient will be assigned a Patient Allocation Number on registration. The Patient Allocation Number and the patient initials are to be entered on the Case Report Form.

11.3 Recording of Data

NCR™ Case Report Forms will be supplied by B.C.I.R.G. or Rhône-Poulenc Research and Development providing a white original and colored copies. These forms must be typewritten or ***PRINTED LEGIBLY*** using black ball-point pen when prepared for submission to B.C.I.R.G. or Rhône-Poulenc Rorer Research and Development.

The forms should be verified against all original records (and workbooks, if applicable) by the B.C.I.R.G. Clinical Monitor before submission. The bottom copy will be retained in the investigator's files, and all other copies will be returned to the B.C.I.R.G. central operational office in [redacted] Canada. No case report forms are to be mailed to the B.C.I.R.G. without specific authorization. Case Report Forms and all original data should be readily available for review during scheduled monitoring visits. Any data to be recorded directly on the Case Report Forms will be considered to be source data.

11.4 Record Retention

1. Copies of all pertinent information will be retained by the investigator for a period of at least 15 years from study completion. Additional considerations must be made about complying with applicable local laws, guidelines, etc.
2. A study document binder will be provided by B.C.I.R.G. for all required study documents. A check list of all records to be retained will be provided by Rhone-Poulenc Rorer.

11.5 Confidential Follow-up

The investigator will be responsible for retaining sufficient information about each patient (e.g. name, address, phone number, social security number/identity number, and identity in the study) so that regulatory agencies or B.C.I.R.G. or Rhône-Poulenc Rorer Research and Development may access this information should the need to do so arise. These records should be retained in a confidential manner for as long as legally mandated according to local requirements.

11.6 Patient Informed Consent (Appendix 6)

Prior to the screening evaluation, the patient will be informed of the nature of the study drug and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient will be exposed will be explained.

An approved informed consent statement will then be read and signed by the patient, and, when required, a witness, and the investigator. The patient will be provided with a copy of the signed informed consent statement. The patient may withdraw from the study at anytime without prejudicing future medical treatment. Verification of a signed informed consent statement will be noted on the patient's study case report form. The investigator will provide Rhone-Poulenc Rorer with an unsigned copy of the informed consent statement prior to and following approval by the appropriate Ethics committee or Institutional Review Board (IRB).

11.7 Ethics Committee/Institutional Review Board

The final approved protocol and the informed consent statement will be reviewed by a properly constituted Ethics Committee/IRB. The Ethics Committee's/Board's decision concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to Rhone-Poulenc Rorer.

Particular attention is drawn to the FDA's regulation regarding the IRBs. By signing the "Statement of Investigator" form (Form 1572), the investigator provides Rhone-Poulenc Rorer with the necessary assurance that an IRB is responsible for the initial and continuing review and approval of the proposed clinical study in accordance with these regulations.

The investigator will agree to make required progress reports to the Ethics committee/IRB, as well as report any serious adverse events, life-threatening problems or deaths. The investigator will also inform the Ethics Committee/IRB of reports of serious adverse events (provided to him/her by Rhone-Poulenc Rorer) in other clinical studies conducted with the study drug. The Ethics Committee/IRB must be informed by the investigator of the termination of the study.

11.8 Declaration of Helsinki

This study is to be performed in accordance with the Declaration of Helsinki (Hong Kong Amendment), as described in Appendix 1.

11.9 Insurance of Liabilities

If required, the investigator may forward the Ethics Committee/IRB a copy of the Insurance that Rhone-Poulenc Rorer has to take out covering his and any other participating parties liabilities.

11.10 Modification of the Protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by Rhone-Poulenc Rorer, the investigator, and approved by the Ethics Committee/IRB prior to implementation and notified to the health authorities in accordance with local regulations.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be agreed upon by Rhone-Poulenc Rorer and the investigator and will be documented in a memorandum. The Ethics Committee/IRB may be notified of administrative changes at the discretion of the investigator.

11.11 Use of Information and Publication

All information concerning the study drug supplied by Rhone-Poulenc Rorer in connection with this study, and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, clinical protocol, workbooks if applicable, Case Report Forms, assay methods, Rhone-Poulenc Rorer's technical methodology, and basic scientific data. This confidential information shall remain the sole property of Rhone-Poulenc Rorer, shall not be disclosed to others without prior written consent from Rhone-Poulenc Rorer and shall not be used except in the performance of this study.

The information developed during the conduct of this clinical study is also considered confidential and will be used by Rhone-Poulenc Rorer in connection with the development of the study drug. This information may be disclosed as deemed necessary by Rhone-Poulenc Rorer.

To allow for the use of the information derived from this clinical study and to insure compliance to current regulations, the investigator is obliged to provide Rhone-Poulenc Rorer with complete test results and all data developed in this study. Only Rhone-Poulenc Rorer may make information obtained during this study available to the physicians and to regulatory agencies, except as required by regulation.

No publication of the study will be made without approval of the advisory board of the B.C.I.R.G. and Rhone-Poulenc Rorer. Rhone-Poulenc Rorer will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. The authorship list will be agreed by the investigators prior to publication. The names on the author list will be given according to the participation in the design of the protocol as well as taking into consideration the input of the number of eligible and evaluable patients accrued by the investigators in each centre. The study will only be published once it is completed and the final analysis has been performed by Rhone-Poulenc Rorer. Interim abstracts will be presented according to the statistical plan and in agreement with Rhone-Poulenc Rorer.

In the event Rhone-Poulenc Rorer chooses to publish the data from this study, Rhone-Poulenc Rorer may provide the advisory board of the study with a manuscript at least 30 days prior to the expected date of submission to the intended publisher.

XII INVESTIGATOR'S AGREEMENT

I have read the preceding protocol

RP 56976 - V - 316

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS 5-FLUOROURACIL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (FAC) AS ADJUVANT TREATMENT FOR OPERABLE BREAST CANCER PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. TAX 316

1. and agree that it contains all necessary details for conducting this study. I will conduct the study as outlined in the preceding protocol and in compliance with GCPs. I will attempt to complete the enrollments into the study by October 1999. I will provide copies of the protocol and all drug information relating to preclinical and prior clinical experience furnished to me by Rhone-Poulenc Rorer, to all physicians responsible to me who participate in this study. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the study. I agree to keep records on all patient information (case report forms and patient's informed consent statement), drug shipment and return forms, and all other information collected during the study in accordance with legal regulations.

_____
Investigator (PRINT NAME)

_____
Investigator Signature Date

_____
Study Medical Coordinator Date

Dr._____

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APPENDIX 1
DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, June 1964,
amended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975,
and
the 35th World Medical Assembly,
Venice, Italy, October 1983
69
and
the 41st. World Medical Assembly, Hong-Kong, September 1989

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

APPENDIX 1 (continued 2)

I BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and Rhone-Poulenc Rorer provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE

(Clinical research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient, including those of a control group, if any, should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician/patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS

(Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the well-being of the subject.

APPENDIX 2

KARNOFSKY INDEX FOR PERFORMANCE STATUS

100	Normal, no complaints: no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self but unable to carry on normal activity or to do work.
60	Requires occasional assistance but is able to care for most of personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalization is indicated although death not imminent.
20	Very ill; hospitalization and active supportive care necessary.
10	Moribund.
0	Dead.

APPENDIX 3
NCI COMMON TOXICITY CRITERIA

	GRADE				
TOXICITY	**0**	**1**	**2**	**3**	**4**
WBC X 10^9/L	≥ 4.0	3.0 - 3.9	2.0 - 2.9	1.0 - 1.9	< 1.0
PLT X 10^9/L	WNL	75.0 - normal	50.0 - 74.9	25.0 - 49.9	< 25.0
Hgb g/dL	WNL	10.0 - normal	8.0 - 9.9	6.5 - 7.9	< 6.5
Granulocytes/ Bands X 10^9/L	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Lymphocytes X 10^9/L	≥ 2.0	1.5 - 1.9	1.0 - 1.4	0.5 - 0.9	< 0.5
Hemorrhage (clinical)	none	mild, no transfusion	gross, 1-2 units transfusion per episode	gross, 3-4 units transfusion per episode	massive > 4 units transfusion per episode
Infection	none	mild	moderate	severe	life-threatening
Nausea	none	able to eat reasonable intake	intake significantly decreased but can eat	no significant intake	--
Vomiting	none	1 episode in 24 hrs	2-5 episodes in 24 hrs	6-10 episodes in 24 hrs	> 10 episodes in 24 hrs or requiring parenteral support
Diarrhea	none	increase of 2-3 stools/day over pre-Rx	increase of 4-6 stools/day, or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence, or severe cramping	increase of ≥ 10 stools/day, or grossly bloody diarrhea or need parenteral support
Stomatitis	none	painless ulcers, erythema, or mild soreness	painful erythema, edema, or ulcers, but can eat	painful erythema, edema, or ulcers, and cannot eat	requires parenteral or enteral support
Bilirubin	WNL	--	< 1.5 x N	1.5 - 3.0 x N	> 3.0 x N
Transaminase (SGOT, SGPT)	WNL	≤2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Alk. Phos. or 5' nucleotidase	WNL	≤ 2.5 x N	2.6 - 5.0 x N	5.1 - 20.0 x N	> 20.0 x N
Liver - clinical	no change from baseline	--	--	precoma	hepatic coma

APPENDIX 3 (continued 2)

	Grade				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Creatinine	WNL	< 1.5 x N	1.5 - 3.0 x N	3.1 - 6.0 x N	> 6.0 x N
Proteinuria	no change	1+ or < 0.3 g% or < 3 g/1	2 - 3+ or 0.3 - 1.0 g% or 3 - 10 g/1	4+ or > 1.0 g% or > 10 g/1	nephrotic syndrome
Hematuria	neg	micro only	gross, no clots	gross + clots	requires transfusion
Alopecia	no loss	mild hair loss	pronounced or total hair loss	--	--
Pulmonary	none or no change	asymptomatic, w. abnormality in PFT's	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
Cardiac dysrhythmias	none	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring or hypotension, or ventricular tachycardia, or fibrillation
Cardiac function	none	asymptomatic decline of resting LVEF less than 20% of baseline value	asymptomatic decline of resting LVEF more than 20% of baseline value	mild CHF, responsive to therapy	severe or refractory CHF
Cardiac-ischemia	none	non-specific T-wave flattening	asymptomatic, ST and T wave changes suggesting ischemia	angina without evidence for infarction	acute myocardial infarction
Cardiac-pericardial	none	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain ECG changes)	symptomatic effusion ; drainage required	tamponade ; drainage urgently required
Hypertension	none or no change	asymptomatic, transient increase by > 20 mm Hg (D) or to > 150/100 if previously WNL. No treatment required	recurrent or persistent increase by > 20 mm Hg (D) or to > 150/100 if previously WNL. No treatment required	requires therapy	hypertensive crisis
Hypotension	none or no change	changes requiring no therapy (incl. transient orthostatic hypotension)	requires fluid replacement or other therapy but not hospitalization	requires therapy and hospitalization resolves within 48 hrs of stopping the agent	requires therapy and hospitalization for > 48 hrs after stopping the agent

APPENDIX 3 (continued 3)

	Grade				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Neuro-sensory	none or no change	mild paresthesias loss of deep tendon reflexes	mild or moderate objective sensory loss moderate paresthesias	severe objective sensory loss or paresthesias that interfere with function	--
Neuro-motor	none or no change	subjective weakness: no objective findings	mild objective weakness without significant impairment of function	objective weakness with impairment of function	paralysis
Neuro-cortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation or hallucinations	coma, seizures, toxic psychosis
Neuro-cerebellar	none	slight, incoor-dination, dys-diadokinesis	intention tremor, dysmetria, slurred speech, nystagmus	locomotor ataxia	cerebellar necrosis
Neuro-mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neuro-headache	none	mild	moderate or severe but transient	unrelenting and severe	--
Neuro-constipation	none or no change	mild	moderate	severe	ileus > 96 hrs
Neuro-hearing	none or no change	asymptomatic, hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neuro-vision	none or no change	--	--	symptomatic subtotal loss of vision	blindness
Skin	none or no change	scattered macular or papular eruption or erythema that is asymptomatic	scattered macular or papular eruption or erythema with pruritus or other associated symptoms	generalized symptomatic macular, papular, or vesicular eruption	exfoliative dermatitis or ulcerating dermatitis
Allergy	none	transient rash drug fever < 38°C, 100.4°F	urticaria, drug fever = 38°C, 100.4°F mild bronchospasm	serum sickness bronchospasm, req. parenteral meds	anaphylaxis
Fever in absence of infection	none	37.1 - 38.0°C 98.7 - 100.4°F	38.1 - 40.0°C 100.5 - 104.0°F	> 40.0°C > 104.0°F for less than 24 hrs	> 40.0°C (104.0°F) for more than 24 hrs or fever accompanied by hypotension

APPENDIX 3 (continued 4)

	Grade				
TOXICITY	**0**	**1**	**2**	**3**	**4**
Local	none	pain	pain with swelling with inflammation or phlebitis	ulceration	plastic surgery indicated
Weight gain / loss	< 5.0%	5.0 - 9.9%	10.0 - 19.9%	≥ 20.0%	--
Hyperglycemia mg/dL	< 116	116 - 160	161 - 250	251 - 500	> 500 or ketoacidosis
Hypoglycemia mg/dL	> 64	55 - 64	40 - 54	30 - 39	< 30
Amylase	WNL	< 1.5 x N	1.5 - 2.0 x N	2.1 - 5.0 x N	≥ 5.1 x N
Hypercalcemia mg/dL	< 10.6	10.6 - 11.5	11.6 - 12.5	12.6 - 13.5	≥ 13.5
Hypocalcemia mg/dL	> 8.4	8.4 - 7.8	7.7 - 7.0	6.9 - 6.1	≤ 6.0
Hypomagnesemia mg/dL	> 1.4	1.4 - 1.2	1.1 - 0.9	0.8 - 0.6	≤ 0.5
Fibrinogen	WNL	0.99 - 0.75 x N	0.74 - 0.50 x N	0.49 - 0.25 x N	≤ 0.24 x N
Prothrombin time	WNL	1.01 - 1.25 x N	1.26 - 1.50 x N	1.51 - 2.00 x N	> 2.00 x N
Partial thromboplastin time	WNL	1.01 - 1.66 x N	1.67 - 2.33 x N	2.34 - 3.00 x N	> 3.00 x N

APPENDIX 4
FLUID RETENTION SEVERITY GRADING

EDEMA	SEVERITY GRADING	EFFUSION
• Asymptomatic *and/or* • Very well tolerated *and/or* • Dependent in evening only	MILD 1	• Asymptomatic • No intervention required
• Moderate functional impairment *and/or* • Pronounced and well tolerated *and/or* • Dependent throughout day	MODERATE 2	• Symptomatic : - exertional dyspnea *and/or* - chest pain *and/or* • ECG changes *and/or* • Abdominal distention • Drainage may be required
• Significant impairment of function *and/or* • Pronounced and not well tolerated *and/or* • Generalized anasarca	SEVERE 3	• Symptomatic effusion - dyspnea at rest *and/or* - tamponade *and/or* - pronounced abdominal distention • Drainage urgently required

⇩

FLUID RETENTION
grading
[MILD, MODERATE, SEVERE]
Reporting the highest grade of edema or effusion

APPENDIX 5
FLOW CHART OF EXAMINATION

Examination	PRESTUDY SCREEN completed no more than (time) prior to registration		DURING THERAPY Every 3 weeks	End of Chemo-therapy	Follow-up
Patient informed consent	before study entry	X			
History	14 days	X			
Physical examination Weight Performance Status	14 days	X	X	X	P
Baseline signs and symptoms	14 days	X			
Adverse events			X	X	X
Hematology Hemoglobin, WBC, neutrophils, platelets	14 days	X	X[1]	X	B
Biochemistry **Liver function** ASAT/ ALAT alkaline phosphatase bilirubin	14 days (Liver function tests repeated within 3 days if abnormal)	X	X (within 3 days prior to chemotherapy)	X	B
Renal function creatinine creatinine clearance (if indicated)	14 days	X	X		
Pregnancy test (urine or serum)	7 days	X			
ECG	3 months	X	as clinically indicated		
LVEF MUGA scan or echocardiography	3 months	X	**Every 12 months**		
Mammography	3 months	X			yearly (year 1-10)
Work up for metastatic disease chest-X-ray abdominal ultrasound or CT scan bone scan	3 months	X			yearly (year 1-5) as clinically indicated
Quality of life	14 days	X	before C3 and C5 (day -1 or day 1)	X	6,12,24 months
Other investigations	as clinically indicated				

X[1] CBC and differential is to be done every three weeks prior to receiving chemotherapy. In case of fever $\geq 38.1°C$, the CBC and differential must be performed and repeated every 2 days until recovery with temperature $< 38.1°C$ or absolute neutrophil count ≥ 0.5

P Physical examination: every 3 months for the first 2 years then every 6 months for years 3-5 then every year for years 6-10.

B Hematology and biochemistry: every 6 months for five years then every 12 months until year 10 or relapse.

APPENDIX 6
SAMPLE PATIENT INFORMED CONSENT - REVISED SEPTEMBER 18, 2006

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS 5-FLUOROURACIL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (FAC) AS ADJUVANT TREATMENT FOR OPERABLE BREAST CANCER PATIENTS WITH POSITIVE AXILLARY LYMPH NODES.

Study number: RP56976- V - 316

Your doctor has explained that you have breast cancer with a risk of relapse. There are several treatments which may help you. We invite you to take part in a research study of a new drug, docetaxel, supplied by Rhône-Poulenc Rorer Research and Development. Taxotere® (docetaxel) has been administered in a total of 575 patients with advanced breast cancer and has been approved for commercial use (as a single agent) for this indication. Preliminary studies suggest that docetaxel in combination with doxorubicin and cyclophosphamide is even more effective in metastatic breast cancer than docetaxel alone. This leads us to try this combination in breast cancer at an earlier stage in the hope that we may prevent or delay relapse.

The aim of the study is to see how effective docetaxel in combination with doxorubicin and cyclophosphamide (TAC) is in your disease compared to a commonly used standard therapy in this situation; 5-fluorouracil in combination with doxorubicin and cyclophosphamide (FAC) which is also an effective treatment in your disease. You will have an equal chance of being treated either TAC or FAC. The decision as to which treatment you receive will be made by chance.

Before receiving the treatment, you will have a number of tests to determine if you can enter the study including a blood examination, a physical examination, an evaluation of your heart function and imaging procedures to check that your disease has not spread to other parts of the body.

While receiving the chemotherapy treatment, you will have your blood checked at least every 3 weeks. These regular blood tests and other examinations will be performed to check that the drugs are not adversely affecting your bone marrow, kidneys, and liver. You should receive the treatment for a duration of 18 weeks (i.e. 6 infusions). Thereafter you will be followed by your physician at the end of the study (one month after the last infusion). You will be prescribed hormonotherapy (tamoxifen) if needed.

Your doctor will then follow you in the same way as other breast cancer patients in order to confirm that the cancer has not relapsed.

For the first 2 years, every three months you will have a physical examination, every 6 months blood tests will be added, and every 12 months mammography and a chest X-ray will be performed.
For years 3 to 5, the 3 month visits will end but the 6 and 12 month visits will continue with the same assessments.
For years 6 to 10, visits will be performed every 12 months including **an evaluation of your heart function and** the full assessments. If at any time you develop signs or symptoms that your doctor feels may be related to cancer, the tests may be performed sooner and additional tests may be ordered.

You will be asked to fill in a quality of life questionnaire before the chemotherapy begins, then every 2 infusions (every 6 weeks) and during the follow-up period (6, 12, and 24 months after end of chemotherapy) about how you feel regarding the treatment of your disease. This will help your doctors to judge the efficacy assessed by medical means against the benefit you feel.
The drugs will be given to you through a drip into a vein in your arm (an infusion) every three weeks.

- 15 minutes for doxorubicin and cyclophosphamide plus 1 hour for docetaxel (TAC)

OR

- 15 minutes for doxorubicin, 15 minutes for 5-fluorouracil, and 5 minutes for cyclophosphamide (FAC)

If you receive docetaxel plus doxorubicin and cyclophosphamide, (TAC), a treatment with oral corticosteroids will be given before each infusion and continued on days 1 and 2 after treatment in order to try to improve certain side effects e.g. allergy reactions, limbs and/or face swelling with or without fluid around lung or abdomen due to docetaxel. You will also take an antibiotic (such as ciprofloxacin) to reduce the risk of infection when your white blood cell count is low.

With docetaxel, you may also experience short lasting mild to moderate nausea and/or vomiting, mouth irritation which may cause you some problems for food intake, diarrhea, fatigue, reversible pins and needles sensation in hands or feet, hair loss, skin reactions, hypotension which needs a close monitoring during infusion. All these side effects were experienced by patients during previous studies and you may also experience other ones which are not predictable at the moment. You will also be asked to weigh yourself weekly to enable your doctor to assess early on if you are developing any fluid retention which can lead to swelling of limbs or fluid around the lungs or abdomen. The infusion itself may cause temporary local irritation and bruises if the drug is infused using a peripheral vein.

If you receive 5-fluorouracil plus doxorubicin and cyclophosphamide, (FAC), you not will require the oral corticosteroids (for side effect of rash and swelling). You will not need the antibiotics unless you develop a problem with fever or infection.

With 5-fluorouracil, you may experience mouth irritation which may impair eating, nausea, vomiting, diarrhea and loss of appetite.

With doxorubicin, you may have the following side effects: blood test changes which may tender you more prone to infection and bruising, mouth irritation which may impair eating, hair loss, nausea and/or vomiting, diarrhea, loss of appetite and fever. If the drug comes in contact with your skin, there may be some skin damage but your doctor and nurses will be careful to avoid this. After a few infusions of doxorubicin, damage to your heart may occur, however, your doctor will monitor you.

With cyclophosphamide, you may experience nausea, vomiting and stopping of the menstrual periods.

These side effects may be a minor inconvenience or could be severe, but the physician in charge of you will watch you closely if any occurs.

In case of fever or bruising after receiving either drug, you must contact doctors in the department.

If you have a fever, your doctor will do some blood work and may prescribe an antibiotic (such as ciprofloxacin). If your white blood cells (cells responsible for fighting infection) are low at the time, your doctor may also prescribe a medication (G-CSF) to stimulate the production of your white blood cells. This would be given as a once daily needle injection.

In case of harm caused to you during the study, Rhône-Poulenc Rorer has contracted an insurance policy which covers the liability of your doctor during the study. You will be informed of any significant new findings about docetaxel which occur during the study and which may lead you to change your willingness to participate.

You should not take part in this study if you think you could be pregnant or if there is a possibility that you could become pregnant during the study. Your doctor will therefore check that you are using a reliable method of contraception before starting your treatment.

Your doctor can remove you from study if it is harmful to you, if you fail to follow treatment instructions, if it is discovered that you do not meet requirements of the trial or if the study is canceled.

In addition to asking you to participate in the above-mentioned study of new treatments for breast cancer, we are asking you to release some of the tumor material taken at the time of your recent surgery(ies) for us to test.

Samples of your tumor tissue will be sent to the headquarters of the Breast Cancer International Research Group (BCIRG) in [redacted], Canada. This material will be used to measure certain markers.

Markers are substances made by breast cancer cells. There will be a number of these measurements, including the ER (estrogen receptor), erbB-2, and p53 which will be made on your tumor material. It is possible that as more information about these research measurements is made available to us during this study, newer markers will also be measured on your tissue sample.

The results of the markers will not be given to you during the course of your participation in this study and may not help you directly even in the future. It will teach us something that we expect will help others in the future.

There are no additional tests required for you to undertake as a result of giving us permission to use this tumor tissue. The BCIRG will keep the samples and use the material in future studies to learn more about breast cancer and other medical problems. The tissue will be used only for research and will not be sold. Some new products could be made because of the results of the research that uses your samples. These products might be sold at some time in the future but you will not be paid.

Your participation in this study is voluntary. If you decide to take part but later change your mind, you are free to do so and do not have to give any reason, however, you should advise your doctor of your decision so he can tell you the procedure to be followed for your medical condition to be properly evaluated and then to continue medical care. The level of care you receive from your doctor will not be affected.

If you participate, your records may be made available to Rhône-Poulenc-Rorer Research-Development (including Quality Assurance representatives), Health Authorities, relevant Regulatory Agencies or may be published for scientific purposes but your identity will remain confidential. Should any problem or question arise with regard to this study, with regard to your rights as a participant in clinical research or with regard to any research related injury, you should contact:

Dr.....tel:.....

PATIENT CONSENT

I have been informed of the purpose, procedures and duration of the study (RP 56976-V-316) with the drug docetaxel plus doxorubicin and cyclophosphamide or 5-fluorouracil plus doxorubicin and cyclophosphamide, of its possible advantages and inconveniences and I agree to participate to this study conducted by Dr..... .

A summary of the information has been given to me.

I know that I am free to refuse to participate and that I can withdraw my consent at any time during the study. I have been given a copy of this consent form to retain.

Name of patient : _____

Signature of patient : _____ date:

Signature of the person witnessing the patient's oral consent (if applicable) : _____ date:

Signature of investigator : _____ date:

APPENDIX 7
ADVERSE EVENT REPORT FORM

1. REACTION INFORMATION

PATIENT INITIALS	STUDY CODE PATIENT N°	COUNTRY	DATE OF BIRTH (DA.MO.YR.)	AGE	SEX	REACTION ONSET (DA.MO.YR.)	CHECK ALL APPROPRIATE TO ADVERSE REACTIONS
							☐ PATIENT DIED ☐ INVOLVED OR PROLONGED IN PATIENT HOSPITALIZATION ☐ INVOLVED SEVERE OR PERMANENT DISABILITY ☐ LIFE THREATENING ☐ NONE OF THE ABOVE

DESCRIBE REACTION(S)
(Give signs or symptoms, diagnoses, course, underline the main event. Include relevant lab. data)

2. SUSPECT RPR DRUG INFORMATION

SUSPECT DRUG (include all information available: Trade name, generic name, form and dosage, batch number. For double blind study, precise if code has been broken.)

DAILY DOSE (with unit)	ROUTE OF ADMINISTRATION
INDICATION FOR USE	
THERAPY DATES (DA.MO.YR.) **from** **to**	**THERAPY DURATION**

DID REACTION ABATE AFTER STOPPING DRUG?
☐Yes ☐No ☐NA*
DID REACTION REAPPEAR AFTER REINTRODUCTION?
☐Yes ☐No ☐NA*
*NA: Not Applicable e.g. only 1 dose or irreversible outcome

3. CONCOMITANT DRUG(S) AND HISTORY

CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (Generic names, exclude those used to treat reaction)

OTHER RELEVANT HISTORY (e.g. diagnoses, allergies, pregnancy with last month of period, etc.)

4. REPORTER OR INVESTIGATOR INFORMATION

NAME AND ADDRESS	REPORT SENT TO LOCAL AUTHORITY ☐Yes ☐No DATE (DA. MO. YR.)	CAUSALITY ASSESSMENT (CONCERNING RPR DRUG) ☐ NOT RELATED ☐ REMOTE ☐ POSSIBLE ☐ PROBABLE	DATE: (DA.MO.YR) SIGNED:

5. ADMINISTRATIVE INFORMATION (RESERVED FOR RPR STAFF)

DATE RECEIVED BY MANUFACTURER (DA.MO.YR.) TRANSMITTED BY:			AFFILIATE CONTROL NUMBER	CONTROL	M.R.A./PHVIG NUMBER		Y	N
						S	☐	☐
						NR	☐	☐
						U	☐	☐
RPR MANUFACTURER			**LOCAL ASSESSMENT (if legally required)**					
DATE OF REPORT (DA.MO.YR.)	**REPORT TYPE** ☐ INITAL ☐ FOLLOW-UP	**REPORT SOURCE** ☐ STUDY ☐ HEALTH PROFES. ☐ LITERATURE ☐ CONSUMER						

APPENDIX 8
PREPARATION GUIDE FOR USE WITH TAXOTERE CONCENTRATE FOR INFUSION AND SOLVENT FOR TAXOTERE

FOR COUNTRIES OUTSIDE EUROPEAN UNION (Ref. to part 10.1.2.1)

1 DRUG SUBSTANCE

- International non-proprietary name: docetaxel
- Code name : RP56976

2 FORMULATIONS

TAXOTERE® concentrate for infusion is a clear viscous, yellow to brown-yellow solution containing 40 mg/mL docetaxel (anhydrous) in polysorbate 80. The Solvent for TAXOTERE® is a 13% w/w solution of ethanol in water for injection.

3 PRESENTATION

3.1 TAXOTERE® 80 mg vial:

- The TAXOTERE® 80 mg vial is a 15 mL clear glass vial with a red flip-off cap.
- The labeled dosage strength is 80 mg docetaxel per vial.
- The labeled volume of one vial is 2 mL of a 40 mg/mL solution of docetaxel in polysorbate 80.
- **Practically, TAXOTERE® 80 mg vial contains 2.36 mL of the 40 mg/mL solution of docetaxel equivalent to 94.4 mg docetaxel. This volume has been established and validated during the development of Taxotere® to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volumes". This overfill ensures that there is a minimal extractable premix volume of 8 mL containing 10 mg/mL docetaxel which corresponds to the labeled amount of 80 mg per vial.**

3.2 solvent for Taxotere® 80 mg vial:

- The Solvent for TAXOTERE ® 80 mg vial is a 15 mL clear glass vial with a transparent colorless flip-off cap.
- The Solvent for TAXOTERE® composition is a 13% w/w solution of ethanol in water for injection
- The theoretical volume of one vial is 6 mL of Solvent for TAXOTERE®.
- **Practically, a solvent for TAXOTERE® 80 mg vial contains 7.33 mL ± 5% of Solvent. This volume has been established and validated based on the practical content of the TAXOTERE® 80 mg vial and ensures a premix concentration of 10 mg/mL docetaxel.**

STORAGE CONDITIONS :

In a refrigerator, protected from bright light.

4 PREPARATION OF THE PREMIX SOLUTION UNDER ASEPTIC CONDITIONS

4.1 Remove the required number of TAXOTERE® 80 mg vials and solvent for TAXOTERE® vials from the refrigerator and allow to stand at room temperature for 5 minutes.

4.2 For each TAXOTERE® 80 mg vial, using a syringe fitted with a needle, withdraw ***THE ENTIRE CONTENTS*** of the corresponding Solvent for TAXOTERE® 80 mg vial (7.33 mL ± 5% for TAXOTERE® 80mg vial) and inject it into the corresponding TAXOTERE® 80 mg vial.

The addition of ***THE ENTIRE CONTENTS*** of one Solvent for TAXOTERE® 80 mg vial to one TAXOTERE® 80 mg vial ensures a minimal extractable volume of the premix solution of 8 mL.

4.3 Remove the syringe and needle and shake the mixture manually for 15 seconds.

4.4 Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation)
The premix solution contains 10 mg/mL docetaxel and is stable for 8 hours in the refrigerator or at room temperature.

5 PREPARATION OF THE INFUSION SOLUTION UNDER ASEPTIC CONDITIONS

5.1 More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use graduated syringes fitted with a needle to withdraw the corresponding premix volume containing 10 mg/mL docetaxel from the appropriate number of premix vials. For example, a dose of 140 mg docetaxel would require 14 mL premix solution.

5.2 Inject the required premix volume into a 250 mL infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution. If a dose greater than 240 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.9 mg/mL docetaxel is not exceeded.

5.3 Mix infusion bag or bottle manually using a rocking motion.

The TAXOTERE® infusion solution should be administered intravenously, as soon as possible after preparation. This should be done as a 1 hour infusion under room temperature and normal lighting conditions.

STORAGE PERIOD :

Premix : 8 hours after reconstitution (at room temperature or in the refrigerator).
Infusion solution : The solution must be used as soon as possible after preparation.

6 VISUAL INSPECTION

As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If TAXOTERE® premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

7 RECOMMENDATIONS FOR THE SAFE HANDLING

TAXOTERE® is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TAXOTERE® solutions. The use of gloves is recommended.

If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

APPENDIX 8

PREPARATION GUIDE FOR USE WITH TAXOTERE CONCENTRATE FOR INFUSION AND SOLVENT FOR TAXOTERE

FOR EUROPEAN UNION : AUSTRIA, BELGIUM, DENMARK, FINLAND, FRANCE, GERMANY, GREECE, IRELAND, ITALY, LUXEMBOURG, NETHERLANDS, PORTUGAL, SPAIN, SWEDEN, UNITED KINGDOM

1. DRUG SUBSTANCE

- International non-proprietary name : docetaxel
- Code name : RP56976

2. FORMULATIONS

TAXOTERE® concentrate for infusion is a clear viscous, yellow to brown-yellow solution containing 40 mg/ml docetaxel (anhydrous) in polysorbate 80. The Solvent for TAXOTERE® is a 13% w/w solution of ethanol in water for injection.

3. PRESENTATION

3.1 TAXOTERE® 80 MG VIAL:

- The TAXOTERE® 80 mg vial is a 15 ml clear glass vial with a red flip-off cap.
- The labeled dosage strength is 80 mg docetaxel per vial.
- The labeled volume of one vial is 2 ml of a 40 mg/ml solution of docetaxel in polysorbate 80.
- **Practically, TAXOTERE® 80 mg vial contains 2.36 ml of the 40 mg/ml solution of docetaxel equivalent to 94.4 mg docetaxel. This volume has been established and validated during the development of Taxotere® to compensate for liquid loss during preparation of the premix (see section 4) due to foaming, adhesion to the walls of the vial and "dead-volumes". This overfill ensures that there is a minimal extractable premix volume of 8 ml containing 10 mg/ml docetaxel which corresponds to the labeled amount of 80 mg per vial.**

3.2 SOLVENT FOR TAXOTERE® 80 MG VIAL:

- The Solvent for TAXOTERE ® 80 mg vial is a 15 ml clear glass vial with a transparent colorless flip-off cap.
- The Solvent for TAXOTERE® composition is a 13% w/w solution of ethanol in water for injection
- The theoretical volume of one vial is 6 ml of Solvent for TAXOTERE®.
- **Practically, a solvent for TAXOTERE® 80 mg vial contains 7.33 ml ± 5% of Solvent. This volume has been established and validated based on the practical content of the TAXOTERE® 80 mg vial and ensures a premix concentration of 10 mg/ml docetaxel.**

STORAGE CONDITIONS :

In a refrigerator, protected from bright light.

4. PREPARATION OF THE PREMIX SOLUTION UNDER ASEPTIC CONDITIONS

4.1. Remove the required number of TAXOTERE® 80 mg vials and solvent for TAXOTERE® vials from the refrigerator and allow to stand at room temperature for 5 minutes.

4.2. For each TAXOTERE® 80 mg vial, using a syringe fitted with a needle, withdraw **THE ENTIRE CONTENTS** of the corresponding Solvent for TAXOTERE® 80 mg vial (7.33 ml ± 5% for TAXOTERE® 80mg vial) and inject it into the corresponding TAXOTERE® 80 mg vial.

The addition of **THE ENTIRE CONTENTS** of one Solvent for TAXOTERE® 80 mg vial to one TAXOTERE® 80 mg vial ensures a minimal extractable volume of the premix solution of 8 ml.

4.3. Remove the syringe and needle and shake the mixture manually for 15 seconds.

4.4. Allow the premix vial to stand for 5 minutes at room temperature and then check that the solution is homogenous and clear. (Foaming is normal even after 5 minutes due to the presence of polysorbate 80 in the formulation).

The premix solution contains 10 mg/ml docetaxel and should be used immediately to prepare the infusion solution.

5. PREPARATION OF THE INFUSION SOLUTION UNDER ASEPTIC CONDITIONS

5.1. More than one premix vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use graduated syringes fitted with a needle to withdraw the corresponding premix volume containing 10 mg/ml docetaxel from the appropriate number of premix vials. For example, a dose of 140 mg docetaxel would require 14 ml premix solution.

5.2. Inject the required premix volume into a 250 ml infusion bag or bottle containing either 5% glucose solution or 0.9% sodium chloride solution.

If a dose greater than 200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/ml docetaxel is not exceeded.

5.3. Mix infusion bag or bottle manually using a rocking motion.

The TAXOTERE® infusion solution should be administered intravenously within the four hours including a one hour infusion under room temperature and normal lighting conditions.

6. VISUAL INSPECTION

As with all parenteral products, TAXOTERE® should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If TAXOTERE® premix solution or infusion solution is not clear or appears to have precipitation, the solution should be discarded.

7. RECOMMENDATIONS FOR THE SAFE HANDLING

TAXOTERE® is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TAXOTERE® solutions. The use of gloves is recommended.

If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with skin, wash immediately and thoroughly with soap and water. If TAXOTERE® concentrate, premix solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

APPENDIX 9

EORTC Quality of Life instruments QLQ-C30 and QLQ-BR23

The English versions of the QLQ-C30 (version 2.0) and QLQ-BR 23 (version 1.0) follow.

Note: The questionnaires are available in all languages of the participating countries.

EORTC QLQ-C30 (version 2.0.)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: (first two letters of first name, first letter of surname)
Your birthdate: (Day, Month, Year):
Today's date: (Day, Month, Year):

		No	Yes
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2.	Do you have any trouble taking a long walk?	1	2
3.	Do you have any trouble taking a short walk outside of the house?	1	2
4.	Do you have to stay in a bed or a chair for most of the day?	1	2
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4

Please go on to the next page

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
16.	Have you been constipated?	1	2	3	4
17.	Have you had diarrhea?	1	2	3	4
18.	Were you tired?	1	2	3	4
19.	Did pain interfere with your daily activities?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21.	Did you feel tense?	1	2	3	4
22.	Did you worry?	1	2	3	4
23.	Did you feel irritable?	1	2	3	4
24.	Did you feel depressed?	1	2	3	4
25.	Have you had difficulty remembering things?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
31.	Did you have a dry mouth?	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4

During the past four weeks:		**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Did you have any pain in your arm or shoulder?	1 2	3	4	
48.	Did you have a swollen arm or hand?	1 2	3	4	
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Was the area of your affected breast swollen?	1 2	3	4	
52.	Was the area of your affected breast oversensitive?	1 2	3	4	
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1 2	3	4	

APPENDIX 10
Pathologic and Molecular Markers for Predicting Clinical Response to Taxotere

Clinical Relevance

The identification of factors which predict Taxotere sensitivity in human tumors will:

1 facilitate the identification of those patients who are likely to respond and lead to the rational integration of Taxotere into clinical practice and
2 point to biological processes/targets which could be co-targeted in combination with Taxotere in order to increase clinical efficacy.

Proposed Study

Little is known about predicting clinical responses to Taxotere. This study will examine those factors which are of known importance in Taxol sensitivity to compare their effect on Taxotere. This includes factors which:

1 predict resistance to Taxol e g. multidrug resistance-1 gene product, ***P-glycoprotein***.
2 are important to the apoptotic mechanism of Taxol induced cell death e.g. ***p53*** and the bcl family ***Bcl-2, Bax, Bcl-X*** and ***Bag-1***.
3 predict for selective chemo-resistance e.g. ***c-erbB-2***

Finally, standard predictors of prognosis will be assessed to see if patients who will benefit from Taxotere can be selected prospectively. These include pathologic grade, histologic subtype, grade and extent of associated in-situ processes, vascular invasion, number of nodes involved, the size of the metastases and the presence of extranodal extension. *Hormone receptors* and the *proliferation index* will also be assessed immunohistochemically.

Methodology

All of the factors noted above in *Italics* will be assayed through immunohistochemistry on a paraffin section block of the primary tumor. The investigation of the Bcl family will be done in collaboration with [redacted] MD, Ph.D., [redacted] All other studies will be performed at the [redacted] using commercially available and well characterized reagents (list available on request). Histopathologic assessment will be performed by a single reference pathologist [redacted] with extensive experience in breast cancer. Interpretation of the immunohistochemical stains will be performed in collaboration with three centers, [redacted] M.D.), [redacted] MD) and the [redacted] MD) for quality control and reproducibility purposes.

The laboratory at the CCI is a reference immunohistochemical lab and the Provincial center for hormone receptor studies (1400/yr) and is well suited for a study of this nature.

Appendix 10 (cont.)

Pathologic examination of the tumor

Due to the well described difficulty in obtaining inter-observer reproducibility [26, 27,28] in the assessment of pathologic factors, only basic pathologic data will be collected from the originating laboratories. *The study design is based on the expectation that all pathologic materials from diagnostic and/or therapeutic procedures will be reviewed by the central lab.* A list of materials and information needed is provided below and a "Pathologic Materials Data Sheet" will be provided separately that will outline the procedures to be followed. The data sheet and pathologic material must be sent within three months of patient randomization.

The pathology materials which must be supplied are:

1. a listing of the original pathology laboratory accession number(s) of all diagnostic and/or therapeutic specimen(s) including biopsy, lumpectomy and/or mastectomy and axillary lymph node dissection. It is not necessary to refer to or include fine needle aspirates or needle core biopsies.
2. a copy of the pathology report on each specimen listed in part 1. Also, a synoptic report must be filled out (included in the "Pathologic Material Data Sheet") and submitted along with the original report.
3. one Hematoxylin and Eosin slide from each block taken on the specimens listed in part 1. These may be recuts as the slides will not be returned.
4. one paraffin block from a representative area of the tumor. The blocks will be kept in the central registry for the duration of the trial. They can be accessed during this period by the original lab. The block will be returned to the original pathology lab at the close of the trial.

The above items should be recorded on the form "Pathologic Material Data Sheet".

As noted elsewhere the pathologic entry criteria for this trial are:

i. the demonstration of invasive adenocarcinoma of the breast with at least one axillary lymph node showing evidence of tumor among a minimum of six resected lymph nodes.
ii. a clear margin which is defined as one in which there is no gross or microscopic evidence of transected tumor.

APPENDIX 11
INFORMATION ON DOXORUBICIN, CYCLOPHOSPHAMIDE AND 5-FLUOROURACIL

1 Information on Doxorubicin

Doxorubicin is an antitumour antibiotic which was first isolated from fermentation broths of S*treptomyces peucetius* var *caesius* .

Doxorubicin is composed of brightly fluorescing tetracyclic chromophore, Adriamycinone which gives the drug its characteristic red color, linked via a glycosidic bond to aminosugar daunosamine.

a) Mechanism of action

Doxorubicin may exert its cytotoxic action by a number of mechanisms:

DNA binding

Doxorubicin intercalates tightly into double stranded DNA leading to local uncoiling of the DNA double helix. Protein associated strand breaks in DNA are produced which are mediated by Topoisomerase II. The local DNA strand damage leads to inhibition of DNA synthesis to a greater extent than RNA [29].

Free radical formation

Reduction of the quinone moiety of the anthracycline molecule leads to further electron transfer to molecular oxygen resulting in free radical species. These free radicals can then cause DNA cleavage, lipid peroxidation, and alkylation of protein and DNA.

Free radicals may be responsible for antitumour activity as well as the cardiac toxicity and mutagenic effect of doxorubicin.

Membrane action

Doxorubicin may react directly with the cell membrane to alter membrane targets function. Doxorubicin can alter the lipid biosynthesis of cardiac cell in vitro, leading to major alterations in membrane composition and function.

b) Drug administration

Intravenous dose of 60 to 90 mg/m² every 3 weeks or 15 to 25 mg/m² weekly, or continuous i.v. of 3 mg/m²/d day 21 to 28 by central venous catheter.

c) Pharmacokinetic data [29]

Distribution

- An intravenous bolus injection of doxorubicin produces high plasma concentrations which fall quickly due to rapid and extensive distribution into tissues.
- Therefore 85 % of plasma doxorubicin is bound to protein leaving 15 to 50% of the total doxorubicin and doxorubicinol as free drug.
- Doxorubicin does not cross the blood brain barrier.

Metabolism

Doxorubicin is rapidly metabolized into:

- The hydrophyllic 13-hydroxyl metabolite: doxorubicinol and the poorly water soluble aglycones: doxorubicinone and 7-deoxydoxorubicinone
- Like doxorubicin, doxorubicinol is cytotoxic, but doxorubicinone is not.
- Metabolism to doxorubicinol occurs by cytoplasmic NADPH dependent aldoketoreductases, present in all cells but particularly in red cells and liver and kidney cells.
- The non-cytotoxic aglycones are formed by an NADPH dependent cytochrome reductase mediated cleavage of the amino sugar moiety in microcosms. This enzymatic reduction of doxorubicin is of paramount importance, as it finally produces the OH radicals [29].

Elimination

- Doxorubicin and its catabolites are primarily excreted in the bile. Over 50 % is eliminated during the first transit through the liver. Only 0.7% to 23% has been recovered in the urine.
- The plasma concentration time curve is characterized by a distribution half life of less than 5 to 10 minutes and a terminal phase elimination half life of 30 $\pm$ 8 hours. A triphasic curve with 3 half lives (12 $\pm$ 8 min, 3.3 + 2, 2 h and 30 $\pm$ 14 h) was also proposed.

d) The main side effects are:

Acute toxicities:

- Extravasation doxorubicin is extremely toxic to tissues when inadvertently extravasated during administration.
- Myelosuppression it is dose related and not cumulative, mainly neutropenia. The nadir values are usually observed during the second week after the infusion and return to baseline by the third week.
- Mucocutaneous reactions mucositis is dose and schedule related (enhanced with infusion).
- Radiation recall reactions doxorubicin can recall radiation effects in previously irradiated fields. Reactions may occur in skin, oral mucosa, heart and lung and may be especially severe in the gastrointestinal tract.
- Dysrhythmias are transient and occur in up to 40 % of patients receiving bolus doxorubicin. They do not appear to be dosage or schedule dependent and do not appear to be related to the development of cardiomyopathy.

Cumulative toxicities:

- Alopecia which is reversible.
- Cardiotoxicity from doxorubicin is thought to result from free radical damage. Patients receiving more than 450 mg/m² of doxorubicin have a 10% risk of developing severe congestive heart failure but subclinical cardiac damage may be detected at $\leq$ 300 mg/m² by radionuclide scans or echocardiography. The cumulative dose above 550 mg/m² increases markedly the risk for clinically evident cardiotoxicity [18].

2 Information on Cyclophosphamide

Cyclophosphamide is an alkylating agent belonging to the group of oxazaphosphorine. It is a pro drug that requires hepatic activation to acquire cytotoxic properties.

Cyclophosphamide is one of the most active drugs used in standard regimen for metastatic breast cancer. In addition, in two comparative studies, cyclophosphamide when used as a single agent was equally effective to CMFVP or CMF-vinblastine [30] when used as single agent (on both intermittent and chronic daily schedules), the response rate ranges between 20% to 35% [30].

Metabolism

To be activated, cyclophosphamide needs to undergo hydroxylation by hepatic cytochromes P450 to form 4 OH cyclophosphamide and aldophosphamide which are considered as a transport form from the liver to the tissue. Two main pathways can then be distinguished:

- Inactivation that yields carboxyphosphamide (the main inactive metabolite in humans).
- Elimination of acrolein that yields phosphoramide mustard (the cytotoxic moiety).

Mechanism of action

- Phosphoramide mustard (the bifunctional alkylating moiety) binds covalently to the DNA, creating crosslinks between DNA strands which leads to cell death.
- Acrolein, does not exhibit any antitumor activity but is responsible for urotoxicity.

Administration

- Cyclophosphamide is administered orally, i.v. or i.m.
- In conventional chemotherapy dosages ranges between 400 to 1200 mg/m².

Pharmacokinetics [31]

- Cyclophosphamide elimination half life ranges from 5 to 8 hours and it is equivalent to the elimination half life of activated metabolites.
- Elimination occurs mainly through hepatic metabolism and only 10% is eliminated in the urine.

Altered physiological conditions

- Hepatic disease might impair the activation of cyclophosphamide in the liver. A longer elimination half life was observed in patients with liver failure, however, there is no clinical evidence that liver dysfunction alters its efficacy or its toxicity. Dosage adjustment is not recommended in the presence of liver dysfunction [31].

The main known complications are:

- Myelosuppression is dose dependent and reversible. Chronic daily administration is usually well tolerated. Sequential administration with an intermediate dose (i.e. 100 to 300 mg/m²/d X 4) is followed by myelosuppression mainly of white cells with a nadir between 7 and 14 days and a duration from 7 to 10 days. Higher doses induce thrombocytopenia and, rarely, anemia.

- Hemorrhagic cystitis (due to acrolein) is prevented by correct hydration with conventional doses. However, mesna is required for higher doses.

- Acute renal toxicity occurs only after high dose regimens and mimics a syndrome of inappropriate secretion of antidiuretic hormone (SIADH - like syndrome). Standard chemotherapy is not toxic for the kidney.

- Acute cardiotoxicity was also described in high dose regimens beyond 1200 mg/kg.

- Other toxicities include Azoospermia and oligospermia (dose related), nausea and vomiting, alopecia.

3 Information on 5-Fluorouracil

Mechanism of action and pharmacology

- 5-Fluorouracil is a fluoropyrimidine that has been extensively investigated. Mechanisms of action include incorporation into cellular RNA and inhibition of DNA synthesis via inhibition of the target enzyme, thymidylate synthase. This drug has no binding to plasma proteins and is eliminated by non-linear kinetic with an $T_{1/2}$ of about 16 minutes.

Administration

- 5-Fluorouracil is administered strictly i.v. either by bolus, short infusion or continuous infusion.

- Usual dosage in polychemotherapy is 500 mg/m^2

The main known complications are

- Myelosuppression with leukopenia usually follows each cycle and is moderate and reversible.

- Stomatitis and esophagopharyngitis are not unusual while diarrhea appears infrequent for doses such as 500 mg/m^2

Alopecia and dermatitis are seen in a substantial number of patients.

APPENDIX 12

Menopausal status definition

Concerning the menopausal status, patients will be classified according to the following definition:

1 = PRE ($\leq$ 6 months since last period AND no prior bilateral ovariectomy AND not on estrogen replacement therapy)
2 = POST (prior bilateral ovariectomy OR >12 months since last period with no prior hysterectomy)
3 = other, age at randomization < 50 years
4 = other, age at randomization $\geq$ 50 years

Definition given according to US NCI funded Cooperative Groups Common Data Elements committee.