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 DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL (AC → T) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER HER2NEU NEGATIVE PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. BCIRG 005

BCIRG Protocol Number: BCIRG 005
SPONSOR Protocol Number: TAX GMA 301

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FINAL VERSION: 17 March 2000
ADMINISTRATIVE CHANGE No 1: 11 September 2000 (France Only)
AMENDMENT No 1: 11 December 2000
AMENDMENT No 2: 17 July 2001
AMENDMENT No 3: 20 August, 2003
AMENDMENT No 4: 17 March 2005

Taxotere® IND 35,555

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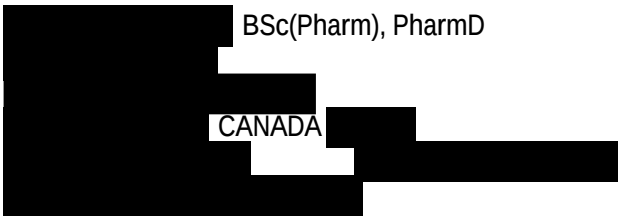

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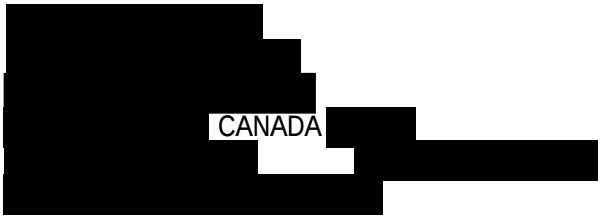

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BCIRG CENTRAL LABORATORY SITES

For Sites in North, South America, Asia, Australia

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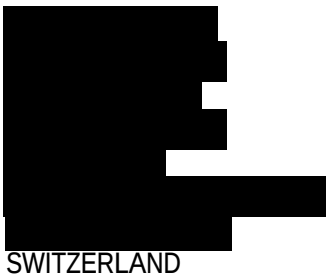

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I STUDY SUMMARY

Title of the Study

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL (AC → T) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER HER2NEU NEGATIVE PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. BCIRG 005

Objectives

Primary objective

To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in operable breast cancer HER2neu negative 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 socioeconomic study will be conducted in parallel with the clinical study.

Study Design and Dosage Regimen

Prospective, non-blinded randomized phase III trial. Three thousand one hundred and thirty patients (3,130) will be post-surgically stratified at inclusion according to center, number of axillary lymph nodes involved (1 to 3; 4 and more) and hormonal receptor status (estrogen and/or progesterone receptor status positive versus negative). They will be randomly assigned to receive either:

TAC x 6: Docetaxel 75 mg/m² as 1 hour IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an IV bolus and cyclophosphamide 500 mg/m² as IV on day 1 every 3 weeks. (Sequence of administration: doxorubicin followed by cyclophosphamide followed by docetaxel.)

ACx4 →T x 4:
Doxorubicin 60 mg/m² as an IV bolus in combination with cyclophosphamide 600 mg/m² as IV followed by docetaxel 100 mg/m² as 1 hour IV infusion 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.

Indication for Hormonal therapy

Tamoxifen (20 mg p.o. daily) for 5 years will be administered starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors.

Patients are allowed to switch to anastrozole in case of tamoxifen related severe toxicities (e.g. hot flushes, vaginal bleeding, vaginal discharge, thromboembolic events). Anastrazole will be given at the dose of 1 mg daily. Of note, the total duration of the

hormonal therapy, i.e. tamoxifen followed by anastrozole, should not exceed 5 years. Only post-menopausal patients are eligible to receive anastrozole.

For post- menopausal women without contraindications to the use of Tamoxifen, a sequential therapy is allowed, consisting of Tamoxifen for 2 to 3 years followed by Anastrozole or exmestane for a maximum of 5 years of hormonal therapy.

Post -menopausal patients who have completed 5 years Tamoxifen are allowed to continue the hormonal treatment with letrozole for a maximum of 3 years

Note: - The use of AIs should be accurately documented and reported on page FU4 of the CRF,

- The same approach is followed for all patients treated in the BCIRG 005/TAX GMA 301 study in order to avoid treatment imbalance between the 2 arms.

- Each center will be requested to provide BCIRG data center with their institution guideline related to the use of aromatase inhibitor by completing a questionnaire.

Indication for Radiation – Either Arm

Patients treated with lumpectomy will undergo postoperative radiation therapy after completion of chemotherapy and resolution of any side effects. 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. Guidelines for postoperative radiation therapy per institution will be collected.

Estrogen and/or Progesterone Receptor Status

Patients must have an analysis of estrogen and/or progesterone receptor on the primary tumor sample. Results must be known prior to randomization. ER-positive tumors can be defined as positive by the Dextran-coated charcoal or sucrose-density gradient method, or positive (using individual laboratory criteria) by the enzyme immunoassay method (EIA), or by immunocytochemical assay. Those not definitively negative i.e "borderline", etc, will also be considered positive.

Patients whose tumor is estrogen receptor negative with progesterone receptor status unknown or undetermined, MUST have the PR assayed in order to determine hormonal receptor status.

Patients whose tumor is progesterone receptor negative with estrogen receptor status unknown or undetermined, MUST have the ER assayed in order to determine hormonal receptor status.

Prophylactic Premedication Regimen

Patients receiving docetaxel in the TAC arm or docetaxel in the AC→T arm will receive the following prophylactic premedication:

Dexamethasone (DXM) or Methylprednisolone (40 mg) or Prednisone (50 mg) or Prednisolone (50 mg) *or equivalent*

Dose, route and schedule

Dexamethasone 8 mg p.o. for 6 doses

1. night before docetaxel.
2. morning of docetaxel.
3. 1 hour before docetaxel infusion.
4. night of docetaxel chemotherapy.
5. morning the day after docetaxel chemotherapy.
6. evening the day after docetaxel chemotherapy.

Prophylactic Antibiotic

TAC Arm Only: Ciprofloxacin 500 mg po twice a day for 10 days starting day 5 of each cycle.

Number of Patients / Enrollment Period / Follow-up Period

Number of patients: 3,130 patients (1,565 patients per arm)

Enrollment period: Enrollment start: August 2000
Enrollment stop: March 2003

Follow-up period: Clinical Follow-up: 10 years

Interim analysis: 50% of events observed (344 events)

Main analysis: 688 events observed

First follow-up analysis: 3 years after the main analysis
Second follow-up analysis: 5 years after the main analysis

Duration of treatment

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

- TAC x 6 cycles
- AC x 4 cycles followed by docetaxel x 4 cycles.

Selection of Patients
Inclusion Criteria

1. Written 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 or equal to 60 days. A central pathology review may be performed post randomization for confirmation of diagnosis and molecular studies. The same block used for HER2neu determination prior to randomization may be used for the central pathology review. See Appendix 3 for details on this process.

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.

5. Tumor must show negative HER2neu proto-oncogene overexpression by FISH. Confirmation of negative overexpression will be centrally assessed by authorized BCIRG laboratories prior to randomization using a paraffin block (see Appendix 3 for complete details).

6. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization. Results must be known at the time of randomization.

(Note: Patients whose tumor is estrogen receptor negative with progesterone receptor status unknown or undetermined, MUST have the PR assayed in order to determine hormonal receptor status. Patients whose tumor is progesterone receptor negative with estrogen receptor status unknown or undetermined, MUST have the ER assayed in order to determine hormonal receptor status.)

7. 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.

8. Karnofsky Performance status index ≥ 80%.

9. Normal cardiac function must be confirmed by LVEF (MUGA scan or echocardiography) and ECG within 3 months prior to registration. LVEF result must be above or equal to the lower limit of normal for the institution. The ECG results must be within normal limits or show no significant abnormalities.

10. Laboratory requirements: (within 14 days prior to registration)

    a) Hematology:
       i) Neutrophils ≥ 2.0 x 10^9/L
       ii) Platelets ≥ 100 x 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 reached, the calculated creatinine clearance should be ≥ 60 mL/min.

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

12. 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.

•13. 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, genetherapy , 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-CTC, version 2.0.

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) carcinoma in situ 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, as no clinical efficacy or safety data are available from phase I-II studies.
16. Current therapy with any hormonal agent such as raloxifene, tamoxifen or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. Patients must have discontinued these agents prior to randomization.

Efficacy Evaluation

- An intent-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 (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix – see Exclusion criteria 9a, 9b) or death from any cause whichever occurs first.
- Survival will be measured from the date of randomization up to the date of death of any cause.

STATISTICAL CONSIDERATIONS

Sample Size Determination

The sample size determination was done based on the following assumptions:
The primary objective of this trial is to show that TAC differs from AC→T in terms of disease free survival (DFS). The following assumptions are made:

- [redacted]

-

A sample of 3,130 patients (1,565 patients per treatment arm) is needed; assuming 3% of patients will be found ineligible after randomization.

The treatment assignment will be based on a dynamic minimization procedure using center, number of axillary lymph nodes involved (1 to 3, 4 and more), hormonal receptor status (estrogen and/or progesterone receptor positive versus negative), as factors in the minimization algorithm, which will use a stochastic treatment allocation based on the variance method.

Updated data on DFS from BCIRG 001 study (TAC Arm) have been used to determine the number of events required for the interim and main analyses by keeping a power of 80% and α =0.05 as originally planned.

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 [2]. 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 [3]. 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 [4].

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 [5].

In the past 10 years, adjuvant hormonal or cytostatic treatment has been increasingly used [6]. Ongoing studies show that adjuvant treatment can prolong time to recurrence and probably survival in some subsets of patients [7,8].

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

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 [9]. They range from CMF chemotherapy of variations to anthracycline containing regimens such as AC, CAF, FAC, AVCF or FEC [10-16]. Numerous randomized trials have compared CMF regimens or variations to anthracycline containing polychemotherapies including FAC [12], initially developed by the CALGB.

The impact of anthracycline-containing polychemotherapy appears real, but modest when compared to other regimens in the adjuvant setting [12-16]. Overall, in both node-negative and node-positive patients, as confirmed by the update of the meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group, adjuvant chemotherapy significantly improves disease-free and overall survival in young patients and to a lesser extent in older patients [8].

Among the novel chemotherapeutic drugs introduced in the 1990's (taxanes, vinorelbine, gemcitabine, 5-fluorouracil prodrugs…), the taxanes have emerged as the most powerful compounds and the available results suggest that they will be remembered in the future as the breast cancer chemotherapy of the 1990's. However, the impact of the taxanes on the natural history of breast cancer is yet to be defined, despite the trend of results suggesting that these agents could have the potential for significant advancement in the management of breast cancer

Two different strategies have been pursued in assessing the potential role of taxanes in adjuvant setting and have led to several large phase III trials. The first strategy is related to the concept of sequential chemotherapy for which both paclitaxel and docetaxel are being investigated. This has led to testing protocols such as the CALGB (Cancer Leukemia Group B) ATC program (A, doxorubicin followed by paclitaxel followed by C, cyclophosphamide) or AC followed by paclitaxel or docetaxel (CALGB; NSABP, National Surgical Adjuvant Breast and Bowel Project) or AT (docetaxel) followed by CMF (Breast Adjuvant Study Team and IBCSG/ International Breast Cancer Study Group) or FEC (5-fluorouracil, epidoxorubicin, cyclophosphamide) followed by docetaxel (French Cooperative Group).

The second strategy follows the classical polychemotherapy concept for which quasi-exclusively docetaxel-based combinations are being studied. Protocols such as TAC (docetaxel) at doses 75/50/500 mg/m^2 have been compared to FAC (Breast Cancer International Research Group, BCIRG trial 001) in patients with node positive breast cancer or AT (docetaxel) at doses 60/60 mg/m^2 to AC (Eastern Cancer Oncology Group, ECOG) in patients with high risk node negative or 1-3 positive nodes. Currently, the only results available comparing a taxane-containing regimen to standard chemotherapy as adjuvant therapy in primary breast cancer comes from the CALGB trial 9344 presented in 1998 [17]. This trial has been initially criticized for its short follow-up (median of 20 months) and the fact that it compared 4 cycles of chemotherapy (AC) versus 8 cycles (AC followed paclitaxel). The results suggest that the sequential addition of paclitaxel to AC may offer improved overall survival and disease-free survival in patients with node-positive primary breast cancer.

In 1999, the first generation of adjuvant trials comparing taxane-anthracycline containing combination to classical anthracycline-containing polychemotherapy were either completed or nearing completion. The trend is now to open the second generation of adjuvant trials with taxanes, in which both arms contain taxanes. The American Intergroup is using the sequential approach and is asking a taxane question, comparing AC followed by either paclitaxel or docetaxel (weekly or 3-weekly). The sequential strategy is being directly compared to the polychemotherapy strategy by NSABP with the B30 trial: AC (60,600 mg/m^2) x 4 followed by docetaxel (100 mg/m^2) x 4 vs AT [60/60 mg/m^2] x 4 vs TAC [60/60/600 mg/m^2] x 4). In this program, a sequence with

8 courses is being compared to 4 courses of docetaxel-doxorubicin based polychemotherapy using the doublet-based docetaxel / doxorubicin at 60/60 mg/m^2 (favoring the increase dose of doxorubicin with 60 mg/m^2 instead of 50 mg/m^2 and decreasing the dose of docetaxel from 75 mg/m^2 to 60 mg/m^2).

2.2.2 Adjuvant Hormonotherapy

The role of adjuvant hormonotherapy was also addressed by the Early Breast Cancer Trialists Cooperative Group [8] and in the NIH Consensus Conference Statement, 2000 [18]. 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 Breast cancer relapse and mortality while in younger women there was benefit seen mostly for odds of Breast cancer 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 Rationale for the use of docetaxel based chemotherapy

2.3.1 Docetaxel as Monochemotherapy

2.3.1.1 Phase II Monochemotherapy

The great majority of phase II studies were performed using docetaxel at a dose of 100 mg/m^2 given over 1 hour every 3 weeks [19-30] while other trials studied 75 mg/m^2 [19, 31-33] and 60 mg/m^2 in Japan [34-36]. The 1-hour schedule and the relatively small difference in doses used in phase II studies probably account for the consistency of results observed throughout the various studies. Phase II data show a significant efficacy for patients with metastatic breast cancer treated with docetaxel 100 mg/m^2 as first-line (response rates ranging from 38% to 68%) [19,20-23] or second-line therapy (response rates from 34% to 58%) [20,24-27] but also for patients previously exposed to anthracyclines (response rates from 29% to 50%) [28-30]. Phase II results with a dose of 75 mg/m^2 q3 weeks show maintained activity with responses rates between 40% and 52% in first-line metastatic [19, 31] and between 44% and 48% in second-line [32,33]. A randomized trial comparing docetaxel 100 mg/m^2 vs 75 mg/m^2 is presently ongoing under the auspices of the European Organization for Research and Treatment of Cancer (EORTC). Toxicity of docetaxel monochemotherapy consists mostly of neutropenia, alopecia, fatigue, mild neurotoxicity and rare allergic reactions. Docetaxel specific toxicities such as nail changes and fluid retention have appeared to be adequately prevented and controlled with 3 days steroid prophylaxis.

2.3.1.2 Phase III Monochemotherapy

With respect to docetaxel, 4 phase III monochemotherapy trials are published or reported to date [37-40]. In the first trial, docetaxel 100 mg/m^2 was compared to doxorubicin 75 mg/m^2 in first line metastatic after failure of alkylating agents [37]. Docetaxel induced more responses than doxorubicin (48% vs 33%, p=0.008), while median time to progression was longer with docetaxel (26 weeks vs 21 weeks, p=ns) although overall survival was identical in both treatment arms. The risk-benefit ratio appeared to favor docetaxel in this trial, suggesting that docetaxel may be more powerful than doxorubicin in first-line therapy of advanced breast cancer.

The 3 other phases III trials were performed in patients with metastatic breast cancer after failure of anthracyclines, comparing docetaxel 100 mg/m^2 given over 1 hour to various salvage regimens [38-40]. The largest study (392 patients) randomized patients between docetaxel and mitomycin-C (12 mg/m^2 q6 weeks) plus vinblastine (6 mg/m^2 q3weeks) [41]. Efficacy was significantly better for docetaxel with higher overall response rate (30% vs 12%, p=0.001), longer time to treatment failure (19 weeks vs 11 weeks, p=0.001) and most importantly longer overall survival (11.4 months vs 8.7 months, p=0.0097). The next study (283 patients) was performed by the Scandinavian group and compared docetaxel to methotrexate plus 5-fluorouracil (5-

FU), respectively 200 mg/m^2 and 600 mg/m^2 day 1 and 8 q.3weeks [39]. Again and confirming the previous trial, efficacy was significantly in favor of docetaxel with better response rates (42% vs 21%, p=0.0001) and longer time to progression (27 weeks vs 13 weeks, p=0.0001). Survival was similar in both arms, possibly related to the built-in crossover design. Finally, the last trial studied, in 172 patients, docetaxel vs NAF (vinorelbine 25 mg/m^2 day 1 and 5 q.3weeks plus continuous infusion 5-FU 750 mg/m^2 over days 1 through 5 q.3weeks). Response rates were 43% for docetaxel and 39% for NAF (p=ns). Time to progression and overall survival were longer with docetaxel (respectively 28 weeks vs 22 weeks and 19.1 months vs 13.9 months), but did not reach statistical significance [40].

All these phase III data are suggesting that docetaxel represent potentially the single most active chemotherapeutic agent for the treatment of breast cancer.

2.3.2 Docetaxel-doxorubicin combinations

Developing combination chemotherapy in the metastatic setting has been a necessary step before proceeding to the adjuvant setting. Among the present polychemotherapies, anthracycline-containing regimens have been established as the chemotherapy of choice in the majority of adjuvant situations, with modest, but real impact on cure rates. In contrast, their role in the long-term improvement of metastatic disease remain elusive.

Given the high individual activity of docetaxel and doxorubicin as single agents in breast cancer, and their potential limited cross-resistance, evidenced by the confirmed activity of docetaxel in patients resistant to anthracyclines, the rationale for the development of combinations based upon these two agents was compelling. Furthermore, the extrahematological toxicity profile of the 2 agents, with limitation of overlapping toxicities, suggested the potentiality for exploitation of the maximum benefit from each agent, in particular in terms of cardiac toxicity.

2.3.2.1 Phase I and II Clinical Trials of Doxorubicin and Docetaxel

A number of trials investigating docetaxel-doxorubicin based combinations have been completed. The results of a dose-finding study in MBC defined the recommended dose when given every 3 weeks as docetaxel 75 mg/m^2 plus doxorubicin 50 mg/m^2, or docetaxel 60 mg/m^2 plus doxorubicin 60 mg/m^2 [41]. Three multi-centered phase II studies have evaluated these recommended doses in first-line metastatic breast cancer (MBC). Dieras et al conducted a phase II trial at a dose level of doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 (A50/T75). Sparano, representing the Eastern Cooperative Oncology Group (ECOG), studied the AT combination at a dose level of doxorubicin 60 mg/m^2 and docetaxel 60 mg/m^2 (A60/T60) [42,43] and Nabholtz explored the three-drug combination TAC, docetaxel 75 mg/m^2 (T), doxorubicin 50 mg/m^2 (A) plus cyclophosphamide 500 mg/m^2 (C) [44]. The TAC regimen was developed with the idea to define a combination which could be, later, randomly compared, in first line metastatic and most importantly in adjuvant setting, to a standard doxorubicin-containing regimen at equivalent doses of doxorubicin (e.g, FAC: 5-fluorouracil, doxorubicin, cyclophosphamide).

The four phase I and phase II studies with the docetaxel and doxorubicin-based combinations have been conducted in first-line MBC. These studies were performed in an outpatient setting with doxorubicin bolus IV infusion separated by either a 15-minute or a 1-hour interval from the docetaxel 1-hour intravenous infusion, on day 1 of a 21-day cycle. A maximum number of cycles of the combination was allowed, but without exceeding the recommended cumulative dose of doxorubicin (500-550 mg/m^2). Patients received concomitant steroid prophylaxis with a 3-day course of dexamethasone 8 mg B.I.D. commencing the day prior to chemotherapy administration. Prophylactic hematopoietic growth factor support and prophylactic antibiotics were prohibited from the Dieras trials. However, all patients in the ECOG trial received prophylactic treatment with a hematopoietic growth factor beginning on day 2 until hematologic recovery and all patients in the TAC trial received prophylactic antibiotic support with ciprofloxacin 500 mg B.I.D. on days 5-15.

Response to therapy: The combination proved to be highly active with the demonstration of consistency in response rates when comparing results between studies. Although phase I studies are not designed for assessing efficacy, responses were seen at all dose levels tested, with an overall response rate of 70% in 40 evaluable patients and a higher overall response rate of 81% noted at the four higher dose levels tested. The combination of docetaxel 75 mg/m^2 plus doxorubicin 50 mg/m^2 (plus

cyclophosphamide 500 mg/m^2) resulted in overall response rates of 74% and 77%, in the phase II trials by Dieras and Nabholtz, respectively. All response rates were reviewed and confirmed by an independent panel. The ECOG study investigating the doublet AT with docetaxel 60 mg/m^2 and doxorubicin 60 mg/m^2 resulted in an overall response rate of 57% in 51 patients. The overall response rate achieved with the A60/T60 dose level is slightly lower in comparison to the A50/T75 dose level, suggesting that maintaining the dose of docetaxel may be important.

Activity in Metastatic Disease Sites: High activity was previously reported with docetaxel single agent in patients with poor prognostic features such as visceral metastases (liver and lung) and 3 or more organs involved. Similar findings were noted with the docetaxel and doxorubicin-based combinations. Overall response rates in the viscera were ranged from 57% to 83% (liver from 80% to 85%, lung from 86% to 90%), and responses were observed in patients with 3 or more organs involved in 84% to 92% of cases.

Time to Progression and 2-Year Survival Rate: The AT or TAC combinations (A: 50/T: 75) are inducing median durations of response ranging from 59 to 62 weeks. As well, median time-to-progression (TTP) was reported to be between 47 to 59 weeks. With more than 2 years median follow up, none of these studies have reached the median survival: the 2-year survival estimates range from 57% to 66%. Results with the doublet AT with docetaxel 60 mg/m^2 and doxorubicin 60 mg/m^2 (ECOG trial) are not yet available.

Safety Profile: The toxicity profile has been consistent throughout the studies. As expected from the combination of two myelosuppressive agents, hematologic toxicity has been prominent. Nearly all patients experienced grade 3/4 neutropenia, however it was generally brief in duration. Febrile neutropenia requiring intravenous antibiotics and/or hospitalizations occurred in 11% to 38% of patients, however documented infections were infrequent and no septic deaths have been reported. Other hematologic toxicities including anemia and thrombocytopenia were infrequent and generally mild to moderate in severity.

When used at doses just below their individual full dose, the non-hematologic toxicities of docetaxel-doxorubicin-based combinations were lower in frequency and milder in severity than when used as individual agents at full dose. Gastrointestinal toxicities were mild, with no grade 3/4 stomatitis, nausea, vomiting or diarrhea reported. Skin and nail toxicities, neurosensory toxicity, and asthenia while frequently noted, were generally mild in severity. Alopecia was universally reported in all studies. Fluid retention secondary to docetaxel was rarely severe and was the cause for treatment discontinuation in only 1 patient in these four studies. The findings support the role of 3-day steroid co-medication to reduce the incidence and severity of fluid retention. Careful attention was given to the effect of docetaxel on the incidence of doxorubicin-induced cardiomyopathy. Despite the administration of a median cumulative total dose of doxorubicin of ranging from 383 mg/m^2 to 401 mg/m^2, the incidence of CHF was no greater than that expected with single agent doxorubicin (0% to 3.5%). None of the patients in the Dieras trials developed CHF. Two patients, in the Sparano and Nabholtz trials respectively, developed CHF, resulting in a 3.5% incidence of CHF. These results suggest a lack of influence of docetaxel on anthracycline-induced cardiomyopathy.

The findings from these trials formed the basis for the conduct of randomized, comparative phase III trials of the docetaxel and doxorubicin-based combinations. Two pivotal trials are either completed and reported (AT versus AC) or nearing completion (TAC versus FAC) in first-line metastatic treatment of breast cancer patients.

2.3.2.2 Phase III Randomized Comparison of AT versus AC

This phase III trial in the first-line treatment of women with MBC compared doxorubicin 50 mg/m^2 plus docetaxel 75 mg/m^2 (AT) to the combination of doxorubicin 60 mg/m^2 plus cyclophosphamide 600 mg/m^2 (AC) [45,46]. The AC regimen has been extensively studied in the adjuvant setting and widely used in both the adjuvant and metastatic settings. The AC regimen uses doxorubicin at a higher dose intensity (doxorubicin 60 mg/m^2 every 3 weeks) than the AT regimen and, despite of this fact, was identified to be appropriate for comparison to the highly active AT combination.

The primary study objective was to compare the time to progression of the two regimens in previously untreated metastatic breast cancer patients. Secondary objectives were to compare response rates, duration of response, toxicity, survival, and quality-of-life between the AT and AC treatment arms. This multi-center international trial was conducted in over 50 centers in

Europe, South Africa, South America, Australia and Canada. No prior chemotherapy for metastatic disease was allowed for these patients with MBC. Patients may have received prior adjuvant chemotherapy with a non-anthracycline containing regimen. As the primary endpoint of this phase III trial was not response rate, entry of patients with both measurable and/or evaluable disease was allowed. The study population was requested to have (see text removed) normal baseline cardiac function (evidence by a normal LVEF), as well as normal hematologic, hepatic and renal function.

In total, 429 patients were randomized to receive treatment with either doxorubicin (50 mg/m^2 15-minute IV bolus infusion) followed in 1-hour by docetaxel (75 mg/m^2 IV infusion over 1 hour), or doxorubicin (60 mg/m^2 15-minute IV bolus infusion) plus cyclophosphamide (600 mg/m^2 15-minute IV bolus infusion). Each cycle of treatment was given on day-1 of a 21-day cycle. Those patients randomized to the AT arm received prophylactic steroid medication with 3-day oral dexamethasone 8 mg B.I.D. Primary prophylactic treatment with oral antibiotics or hematopoietic growth factors (i.e. G-CSF or GM-CSF) was not allowed. However, G-CSF administration was permitted for the treatment of febrile neutropenia or documented infection, and for prophylaxis in subsequent cycles for patients experiencing febrile neutropenia or infection during an earlier cycle.

Of the 429 randomized patients, a total of 423 patients were treated, with 213 in the AT arm, and 210 in the AC arm. The two treatment groups were well balanced for age, performance status, prior adjuvant chemotherapy exposure and disease-free interval. Extent of disease and involved disease sites were also comparable in both treatment groups. Both regimens proved feasible for delivery of therapy. Patients randomized to the AT arm received a median of 8 cycles of the combination with a relative dose intensity (RDI) of 0.97. The median cumulative dose of doxorubicin and docetaxel delivered was 378 mg/m^2 and 552 mg/m^2, respectively. Patients randomized to the AC arm received a median of 7 cycles of the combination with a RDI of 0.96, and a median cumulative dose of doxorubicin of 420 mg/m^2 and a median cumulative dose of cyclophosphamide of 4198 mg/m^2.

On an intent-to-treat basis, response rate information indicates a higher overall response rate and a higher complete response rate in favor of the AT regimen. The overall response rate was 60% for the AT group, versus 47% for the AC group. These findings are highly statistically significant, with a p-value of 0.0153. In addition, an improvement in complete response rate was noted for the AT regimen. A complete response was documented in 11% of AT patients, in comparison to 8% of AC patients. Of the remaining patients, progressive disease was documented in 8% of AT patients, versus 18% of AC patients. Multivariate analysis confirms the significant superiority of the AT combination over AC. Additionally, these findings were maintained in patients with unfavorable prognostic factors, such as visceral involvement, multiple disease site involvement and exposure to prior adjuvant chemotherapy. Time-to-progression (TTP) and time to treatment failure (TTF) were significantly longer with AT compared to AC (p= 0.012 and p=0.0295 respectively). Overall survival results are pending at the present time.
The safety profile of both regimens showed that the main grade 3/4 adverse events for both treatment arms are hematologic in nature and are mostly related to grade 3/4 neutropenia and febrile neutropenia. However, febrile neutropenia was infrequently complicated by infection and resulted in septic death in one patient only from the AC arm. Non-hematologic grade 3/4, or serious toxicities occurred in less than 10% of patients and were well balanced between the 2 treatment arms. They included mucositis, diarrhea, and asthenia. Of note was the low frequency of docetaxel specific toxicities (fluid retention, nail changes…) as previously noted in clinical trials of single agent docetaxel. Premedication with a 3-day steroid prophylaxis prevented the development of severe edema in all but 1% of patients in the AT arm, despite a median cumulative dose of docetaxel of 552 mg/m^2. Of interest was the infrequent observation of cardiomyopathy despite the delivery of a median cumulative doxorubicin dose of more than 360 mg/m^2 in 54% of patients in the AT treatment arm. At a median of 18 month follow-up, the incidence of CHF was 3% for patients in the AT arm, and slightly higher at 4% for patients in the AC arm. Decline in LVEF by 30-points from baseline was noted in 1% of patients evaluated in the AT arm, and in 6% of patients evaluated in the AC arm. These results confirm the findings from phase II trials and support the lack of influence of docetaxel on doxorubicin-induced cardiomyopathy.

2.4 Rationale for the Present Adjuvant Trial

The adjuvant trials represent the ultimate setting for testing new and promising chemotherapy combinations and address the potential for cure. The subjectiveness 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. 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. 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.

Two different strategies have been pursued in assessing the potential role of taxanes in adjuvant setting and have led to several large phase III trials. The first strategy is related to the concept of sequential chemotherapy for which both paclitaxel and docetaxel are being investigated. This has led to testing protocols such as ATC program (A, doxorubicin followed by paclitaxel followed by C, cyclophosphamide) or AC followed by paclitaxel or docetaxel or AT (docetaxel) followed by CMF, or FEC (5-fluorouracil, epidoxorubicin, cyclophosphamide) followed by docetaxel. The second strategy follows the classical polychemotherapy concept for which quasi-exclusively docetaxel-based combinations are being studied. Protocols such as TAC (docetaxel) at doses 75/50/500 mg/m^2 have been compared to FAC (Breast Cancer International Research Group, BCIRG trial 001) in patients with node positive breast cancer or AT (docetaxel) at doses 60/60 mg/m^2 to AC (ECOG) in patients with high risk node negative or 1-3 positive nodes.

In 1999, the first generation of adjuvant trials comparing taxane-anthracycline containing combination to classical anthracycline-containing polychemotherapy were either completed or nearing completion. The trend is now to open the second generation of adjuvant trials with taxanes, in which both arms contain taxanes.

One of the main questions in the adjuvant setting is related to the direct comparison of both strategies (sequence vs polychemotherapy). The sequential strategy is being directly compared to the polychemotherapy strategy by NSABP with the B30 trial: AC (60,600 mg/m^2) x 4 followed by docetaxel (100 mg/m^2) x 4 vs AT [60/60 mg/m^2] x 4 vs TAC [60/60/600 mg/m^2] x 4). In this program, a sequence with 8 courses is being compared to 4 courses of docetaxel-doxorubicin based polychemotherapy using the doublet-based docetaxel / doxorubicin at 60/60 mg/m^2 (favouring the increase dose of doxorubicin with 60 mg/m^2 instead of 50 mg/m^2 and decreasing the dose of docetaxel from 75 mg/m^2 to 60 mg/m^2).

We are proposing in our trial to compare a potential optimal polychemotherapy, using 6 courses of TAC with the doses of docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2, to the classical sequence AC (60,600 mg/m^2) x 4 followed by docetaxel (100 mg/m^2) x 4.

Because this study will be run in tandem with the BCIRG 006 study that is assessing Taxotere® combinations with Herceptin in HER2neu positive patients, we propose that the BCIRG 005 study be performed in HER2neu non-overexpressors.

2.5 Methods to Detect HER2neu Overexpression

Pathologic HER2neu overexpression in human breast cancers is almost invariably due to amplification of the HER2neu gene [47, 48]. Less than 5% of breast cancers show overexpression without gene amplification. Currently, the most frequently performed assay for assessment of HER2neu status is immunohistochemistry. However, HER2neu immunohistochemistry, especially as performed with FDA-approved assays, is known to have a high rate of both false-positive and false-negative results that are at least in part dependent on the subjective interpretation of the assay in different laboratories. More over, recent data have shown that patients amplifying the oncogene HER2neu (FISH positive) were the only ones likely to benefit from Herceptin based therapy. The relationship between HER2neu overexpression and c-erbB2 amplification as measured by FISH was analysed using 623 clinical specimens with a forced 1:1 ratio of positive (2+/3+) to negative (0/1+) results by the Clinical Trials Assay (CTA), 317 CTA+ and 306 CTA- [49]. These specimens were then analyzed by FISH. The amplification rates by CTA

score were 3+, 89.3%; 2+, 23.9%; 1+, 6.7%; 0, 4.2%. The overall 2x2 concordance between the CTA and FISH was 81.3%. The relationship between c-erbB2 amplification status and Herceptin clinical benefit was then evaluated in 3 pivotal trials. In study H0648g, the addition of Herceptin to chemotherapy (AC or paclitaxel) resulted in a response rate of 54% versus 27% with chemotherapy alone and a 50% increase in median survival (27 months versus 18 months) for the FISH positive subgroup. The FISH negative subgroup showed no improvement in response rate (41% versus 39%) and no improvement in survival (24 months versus 20 months). In H0649g, response rate in the FISH positive subgroup was 20%. No responses were seen in the FISH negative subgroup including 17 patients demonstrating a 3+ CTA score. In H0650g, the FISH positive subgroup showed a 41% response rate while the FISH negative subgroup demonstrated a 5% response rate (1 patient).

The proper selection of the patient population has become of utmost importance. FISH has been shown to be the best test for detecting the presence or absence of the HER2neu alteration in human breast cancer specimens. BCIRG has thus decided to use the FISH method of identifying patients for entry into this adjuvant trial. The fluorescence in situ hybridization (FISH) procedure will be performed in centralized laboratories to select women for this clinical trial.

2.6 Justification of Central Pathology Review

A central pathology review will be performed on sections derived from the paraffin block submitted for FISH testing. We will confirm the baseline tumor characteristics of all patients randomized into the study in a single central laboratory to avoid issues of inter-laboratory comparability. Standard prognostic histo-pathologic features such as grade, histologic subtype and vascular invasion as well as immunohistochemical markers for hormone receptors, and proliferation index (MIB-1) will be recorded. This review will take place after randomization. Blocks will also be requested for confirmation of the histopathologic diagnosis of a new breast malignancy or second primary cancer.

Some markers may be considered predictors of response to certain anticancer agents (see Appendix 3). By predetermining the biological characteristics of a patient's tumor, therapies may be specifically targeted to those patients whose tumor has a characteristic that predicts an increased response to the anticancer agent. The FISH test is able to predict the type of tumor that will benefit from the agent Herceptin, for example (see section 2.5).

2.6.1 Mandatory Tests on Tumor Sample

In addition to the FISH testing prior to randomization, a central pathology review will be performed on sections derived from the paraffin block submitted for FISH testing.

2.6.2 Optional Tests on Tumor Sample

The remaining tests are not mandatory.

Additional testing for such markers on the tumor sample is proposed. These markers include: p53, members of the bcl family (Bcl-2, bax, Bcl-X and Bag-1), MUC1 and Tubulin isoforms (particularly II, III, IV and Tau). Those factors, which are proven to have predictive utility in that trial, will be tested in the current trial in order to ensure comparability between groups.

The area of research into the identification of tumor markers and biological processes / targets to aid in the identification of clinical benefit in certain subsets of populations or even in the identification of anticancer therapies to target the marker, is rapidly growing. Following the mandatory FISH testing and central pathology review for the study, BCIRG wishes to store the tumor sample for future testing. As more development and information is revealed to us in the future, we would like to use these blocks for measurement of the new markers. The blocks will be stored in the central laboratory until future use is required. BCIRG may collaborate in the future with experts in the field, and the blocks (or portions thereof) may be shared with other researchers. A current example of this is the collaboration with [redacted] who is researching the blocks for the Bcl family.

Although the tumor block is mandatory for the FISH and central pathology review, testing for the designated tumor markers and future testing is not mandatory. Refusal to grant permission for further testing will not affect the quality of care the participant is to receive.

III STUDY OBJECTIVES

Primary:

To compare disease-free survival after treatment with docetaxel in combination with doxorubicin and cyclophosphamide (TAC) to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) in operable adjuvant breast cancer HER2neu negative 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.

To evaluate pathologic and molecular markers for predicting efficacy (Appendix 3).

An independent socioeconomic 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 multi-center, international study involving 3,298 patients. Enrollment starts in August 2000 and stopped in February 2003 with a follow-up period of 10 years. The interim analysis is planned when 50% of events have been observed (344 events). The main analysis is planned when 688 events have been observed. The follow-up analyses will take place respectively 3 years and 5 years after the main analysis.

4.2 Duration of Treatment

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

TAC: 6 cycles.

AC → T: 4 cycles of AC followed by 4 cycles of docetaxel single agent.

4.3 Inclusion Criteria

1. Written 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 or equal to 60 days. A central pathology review may be performed post randomization for

confirmation of diagnosis and molecular studies. The same block used for HER2neu determination prior to randomization may be used for the central pathology review. See Appendix 3 for details on this process.

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.

5. Tumor must show negative HER2 neu proto-oncogene overexpression by FISH. Confirmation of nonoverexpression will be centrally assessed by authorized BCIRG laboratories prior to randomization.

6. Estrogen and/or progesterone receptor analysis performed on the primary tumor prior to randomization. Results must be known at the time of randomization.

(Note: Patients whose tumor is estrogen receptor negative with progesterone receptor status unknown or undetermined, MUST have the PR assayed in order to determine hormonal receptor status. Patients whose tumor is progesterone receptor negative with estrogen receptor status unknown or undetermined, MUST have the ER assayed in order to determine hormonal receptor status).

7. 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.

8. Karnofsky Performance status index ≥ 80%.

9. Normal cardiac function must be confirmed by LVEF (MUGA scan or echocardiography) and ECG within 3 months prior to registration. LVEF result must be above or equal to the lower limit of normal for the institution. The ECG results must be within normal limits or show no significant abnormalities.

10. Laboratory requirements: (within 14 days prior to registration)

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

~~ii)~~b) Hepatic function:
- ~~13.~~i) Total bilirubin ≤ 1 UNL
- ~~14.~~ii) ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 UNL
- ~~15.~~iii) Alkaline phosphatase ≤ 5 UNL
- ~~16.~~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.

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

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

12. 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.

13. 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, genetherapy , 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-CTC, version 2.0.
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) carcinoma in situ 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, as no clinical efficacy or safety data are available from phase I-II studies.
16. Current therapy with any hormonal agent such as raloxifene, tamoxifen or other selective estrogen receptor modulators (SERMs), either for osteoporosis or prevention. Patients must have discontinued these agents prior to randomization.

V PLAN OF THE STUDY

This is a prospective, ***non-blinded***, ***randomized***, phase III trial. Patients will be post surgically stratified at inclusion according to the center, the number of axillary lymph nodes involved (1 to 3; 4 and more), hormonal receptor status (estrogen and/or progesterone receptor status positive versus negative and will be randomly assigned to one of two groups and receive either:

- TAC: Docetaxel 75 mg/m² as 1 hour IV infusion on day 1 every 3 weeks in combination with doxorubicin 50 mg/m² as an IV bolus and cyclophosphamide 500 mg/m² as IV on day 1 every 3 weeks. Six cycles of TAC are to be administered. Sequence of administration is as follows: doxorubicin followed by cyclophosphamide followed by Taxotere®.

- AC → T: Doxorubicin 60 mg/m² as an IV bolus in combination with cyclophosphamide 600 mg/m² as IV for 4 cycles followed by single agent docetaxel 100 mg/m² as 1 hour IV infusion on day 1 every 3 weeks for 4 cycles.

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 Indication for Hormonal therapy:

Tamoxifen (20 mg p.o. daily) for 5 years will be administered starting 3 to 4 weeks after the last course of chemotherapy for patients with positive estrogen and/or progesterone receptors.

Patients are allowed to switch to anastrozole in case of tamoxifen related severe toxicities (e.g. hot flushes, vaginal bleeding, vaginal discharge, thromboembolic events). Anastrazole will be given at the dose of 1 mg daily. Of note, the total duration of the hormonal therapy, i.e. tamoxifen followed by anastrozole, should not exceed 5 years. Only post-menopausal patients are eligible to receive anastrozole.

For post -menopausal women without contraindications to the use of Tamoxifen, a sequential therapy is allowed, consisting of Tamoxifen for 2 to 3 years followed by Anastrozole or Exmestane for a maximum of 5 years of hormonal therapy.

Post- menopausal patients who have completed 5 years Tamoxifen are allowed to continue the hormonal treatment with letrozole for a maximum of 3 years

Note: - The use of AIs should be accurately documented and reported on page FU4 of the CRF,

- The same approach is followed for all patients treated in the BCIRG 005/TAX GMA 301 study in order to avoid treatment imbalance between the 2 arms.

- Each center will be requested to provide BCIRG data center with their institution guideline related to the use of aromatase inhibitor by completing a questionnaire.

- 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. Guidelines for postoperative radiation therapy per institution will be collected

Estrogen and/or Progesterone Receptor Status

Patients must have an analysis of estrogen and/or progesterone receptor on the primary tumor sample. Results must be known prior to randomization. ER-positive tumors can be defined as positive by the Dextran-coated charcoal or sucrose-density gradient method, or positive (using individual laboratory criteria) by the enzyme immunoassay method (EIA), or by immunocytochemical assay. Those not definitively negative i.e "borderline", etc, will also be considered positive.

Patients whose tumor is estrogen receptor negative with progesterone receptor status unknown or undetermined, MUST have the PR assayed in order to determine hormonal receptor status.

Patients whose tumor is progesterone receptor negative with estrogen receptor status unknown or undetermined, MUST have the ER assayed in order to determine hormonal receptor status.

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

For the purpose of this study, study medication will be defined as the combination of chemotherapy in each of the study arms for the duration of the active treatment. For those patients receiving hormonal therapy as per protocol, such treatment will not be considered in the definition of study medication.

5.1.1 TAC Docetaxel in Combination with Doxorubicin and Cyclophosphamide

Doxorubicin will be given first

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

followed by
Cyclophosphamide

Dose: 500 mg/m², day 1
Route: 5 to 60 minutes intravenous (as per hospital guidelines)
Schedule: every 3 weeks

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*.

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

5.1.2 AC followed by docetaxel (AC → T)

AC →T will consist of 4 cycles of AC followed by 4 cycles of docetaxel:

AC:

Doxorubicin will be given first

Dose: 60 mg/m², day 1
Route: 15 minutes intravenous bolus injection
Schedule: every 3 weeks

followed by
Cyclophosphamide

Dose: 600 mg/m², day 1
Route: 5 minutes to 60 minutes intravenous as per hospital guidelines
Schedule: every 3 weeks

This is called *a cycle of treatment*. *Given 4 times* (for administration to patients see section 11.1.2).

Docetaxel:

Three weeks after the last course of AC, docetaxel will be given

Dose: 100 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*. *Given 4 times* (for administration to patients see section 11.1.2).

Please note that if the treatment cannot be given within the time frame accepted in the protocol, the patient should however be treated with the treatment assigned during randomization unless clinically contraindicated.

5.1.3 Prophylactic Antibiotic Therapy

TAC Arm

Prophylactic antibiotic therapy must be administered to patients randomized to the TAC arm.

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

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.

AC → T Arm

Patients randomized to and treated with this arm will use prophylactic antibiotics for all cycles *only subsequent* to experiencing an episode of severe infection, grade 3 or 4 (see section 5.2.2). Ciprofloxacin as above is recommended.

5.1.4 Prophylactic Premedication Regimen for Fluid Retention

The following prophylactic premedication regimen must be administered for all patients treated with docetaxel in the TAC arm and docetaxel in the AC → Taxotere® arm (Taxotere® segment only).

Dexamethasone (DXM) or Methylprednisolone (40 mg) or Prednisone (50 mg) or Prednisolone (50 mg) *or equivalent*

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

1. night before docetaxel chemotherapy
2. immediately upon waking the morning of docetaxel chemotherapy
3. one hour before infusion of docetaxel
4. night of docetaxel chemotherapy
5. morning the day after docetaxel chemotherapy
6. evening the day after docetaxel chemotherapy

5.1.5 Anti-emetic Treatment

A prophylactic anti-emetic treatment is mandatory in both arms. The use of a $5HT_3$-antagonist is strongly recommended. However, the type of treatment (metoclopramide, ondansetron, granisetron, etc.) is at the discretion of the investigator.

5.2 Treatment Delay and Dose Reduction / Modification

5.2.1 Treatment Delays

Treatment with chemotherapy may be delayed no more than 2 weeks (up to Day 35) to allow recovery from acute toxicity.

5.2.2 Treatment Dose Adjustments

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

AC→T: 60 mg/m² for doxorubicin and 600 mg/m² for cyclophosphamide, then 100 mg/m² for docetaxel.

Dose reduction is planned for each arm in case of severe hematological and/or non-hematological toxicities as follows:

- AC→T Arm
  Doxorubicin: from 60 mg/m² to 50 mg/m²
  Cyclophosphamide: from 600 mg/m² to 500 mg/m²
  Docetaxel Single Agent: from 100 mg/m² to 75 mg/m²

- TAC Arm
  Docetaxel in Combination: from 75 mg/m² to 60 mg/m²
  Doxorubicin: from 50 mg/m² to 40 mg/m²
  Cyclophosphamide: from 500 mg/m² to 400 mg/m²

Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Toxicities will be graded using the NCI common toxicity criteria, version 2.0 (see Appendix 13).

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 in the case of liver function tests that improve within ranges given.

5.3 Toxicity Related Guidelines for Dose Adjustments in Both Arms

5.3.1 Hematological Toxicities

5.3.1.1 Febrile Neutropenia

Febrile neutropenia shall be defined as oral or tympanic fever of ≥ 38.5° C or 101.3 ° F in the presence of neutropenia (where neutropenia is defined as ANC < 1.0×10^9 /L). See NCI CTC, version 2.0 (Appendix 13).

A therapeutic intervention should proceed immediately following the diagnosis of febrile neutropenia. Therapeutic interventions may include:

- hospital admission
- pre-antibiotic evaluation
- CBC with differential and blood culture should be performed
- start of an empirical antibiotic therapy

In case of febrile neutropenia, blood counts must be done every 2 days until recovery of ANC ≥ 1.0 x 10^9/l or temperature < 38.5°C. This must be documented in the CRF for Febrile Neutropenia.

For all subsequent chemotherapy cycles, prophylactic G-CSF will be added as per guidelines outlined in section 5.3.1.5. Addition of antibiotics as prophylaxis for febrile neutropenia is not recommended for the AC→T arm. Ciprofloxacin or equivalent oral antibiotic should continue in the TAC arm as outlined in section 5.1.3.

5.3.1.2 Infection With (or Without) Neutropenia

For severe (Grade 3) or life-threatening (Grade 4) infection during chemotherapy in the AC→T arm, with or without neutropenia, prophylactic G-CSF and prophylactic antibiotics will be added to all remaining cycles. Prophylactic G-CSF will be added to all remaining cycles of the TAC arm, and the prophylatic oral antibiotic will continue.

Ciprofloxacin is recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles. If ciprofloxacin is not available or not tolerated, another oral antibiotic must be used. The choice of antibiotic is at the discretion of the investigator.

G-CSF will be added to all subsequent chemotherapy cycles as per guidelines outlined in section 5.3.1.5.

5.3.1.3 2nd Febrile Neutropenia and 2nd Infection Event

In the case of a second febrile neutropenia event or 2nd infection episode, patient will continue with the prophylactic G-CSF for all subsequent cycles. In addition, all chemotherapeutic drug doses will be reduced as outlined in Section 5.2.2 Treatment Dose Adjustments.

In the case of a 3rd event, there will be no further dose reduction. Patient will go off study into regular follow-up.

5.3.1.4 Delayed ANC Recovery on Day 21

BLOOD COUNTS ON DAY 21

Neutrophils (x 10^9/L)	Action to be taken
≥ 1.5	Treat on time
< 1.5	1. CBC should be repeated every other dayuntil day 35 · Proceed with full dose chemotherapy as soon as ANC ≥ 1.5. - Consider curative treatment with GCSF. · Add G-CSF in remaining cycles if recovery occurred after day 28. 2. If there is no recovery on day 35, (ANC < 1.5 x 10^9/L), the patient will go off chemotherapy.

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

a) 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 5.3.1.4).
- At investigator discretion, primary prophylaxis (i.e. from 1st cycle onwards) for either arm will be allowed but is not mandatory

b) Dose and Schedule for G-CSF Prophylaxis

Dose: 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 for 7 days 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.
If the ANC 1.0 X 10^9 / L, then injections will stop.
If the ANC < 1.0 X 10^9 / L, then injections will continue to complete 10 days of therapy, day 13 inclusive.

5.3.1.6 Thrombocytopenia

The following dose adjustments are based on the hematologic counts on the day of or day prior to chemotherapy treatment.

Platlet Count (cells/μL)	AC→T or TAC
≥100,000	No change
<100,000	Hold for a maximum of 2 weeks. If during AC, reduce doxorubicin from 60 to 50 mg/m² If during docetaxel, reduce docetaxel from 100 to 75 mg/m² If during TAC, reduce docetaxel from 75 to 60 mg/m² If after 2 weeks, and no recovery above 50,000, all chemotherapy is permanently discontinued. If after 2 weeks, recovery above 50,000, treat with dose reduction above for all subsequent doses.

5.3.1.7 Anemia

In case of ≥ grade 2 decrease in hemoglobin, treatment with blood transfusion or erythropoietin should be given.

In the case where the next cycle of chemotherapy is due, chemotherapy to be administered if hemoglobin is > 10 g/dl.

In case of ≥ grade 3 or 4 decrease in hemoglobin, doses should be reduced as follows:

If during docetaxel as single agent in AC→T, docetaxel dose to be decreased from 100 to 75 mg/m^2.

If during TAC, docetaxel to be reduced from 75 to 60 mg/m^2.

5.3.2 Non Hematological Toxicities

5.3.2.1 Nausea and Vomiting

A prophylactic anti-emetic treatment is mandatory in both arms. The use of a $5HT_3$-antagonist is strongly recommended. However, the type of treatment (metoclopramide, ondansetron, granisetron, etc.) is at the discretion of the investigator.

5.3.2.2 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/m^2 (TAC) or from 100 to 75 mg/m^2 (AC→T) in the docetaxel segment. If despite dose reduction, diarrhea still occurs at grade ≥ 3, the patient will go off chemotherapy as per investigator discretion. In case of diarrhea ≥ grade 3 in the AC segment of AC→T, reduce the dose of doxorubicin from 60 to 50 mg/m^2. If despite dose reduction, diarrhea still occurs at grade ≥ 3, the patient will go off chemotherapy as per investigator discretion.

5.3.2.3 Stomatitis

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

- TAC: docetaxel will be reduced from 75 to 60 mg/m^2. If despite dose reduction, stomatitis still occurs at grade ≥ 3, doxorubicin will be reduced from 50 to 40 mg/m^2. No further dose reduction is planned.

- AC→T: During the AC segment, doxorubicin will be reduced from 60 to 50 mg/m^2. If despite dose reduction, stomatitis still occurs at grade ≥3, doxorubicin will be reduced from 50 to 40 mg/m^2. No further dose reduction is planned. If during the docetaxel segment, docetaxel will be reduced from 100 to 75 mg/m^2. If despite dose reduction, stomatitis still occurs at grade ≥ 3, docetaxel will be further reduced from 75 to 60 mg/m^2. No further dose reduction is planned.

5.3.2.4 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/m^2) will apply for this study.

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

ASAT / ALAT values and Values	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 AC→T: AC Reduce dose of doxorubicin from 60 to 50 mg/m² T Reduce dose of docetaxel from 100 to 75 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 AC→ T: AC Reduce dose of doxorubicin from 60 to 50 mg/m² T Reduce dose of docetaxel from 100 to 75 mg/m²
> 5 x UNL	> 5 x UNL	Both Arms: Dose delay by a maximum of 2 weeks. If no recovery to the above, patient should go off chemotherapy.

Once the dose has been reduced due to impaired liver function, no further dose reduction is recommended if worsening of the parameters is no longer observed. In case of worsening patient will go off chemotherapy.

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

5.3.2.5 Peripheral neuropathy

Please refer to Appendix 13 for "neurosensory" and "neuromotor" criteria.

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 Arm
Delay chemotherapy treatment by maximum of two weeks.
As soon as patient recovers, treatment should continue with the following dose recommendations:

If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 75 to 60 mg/m².
If grade ≥ 2 persists for > 2 weeks, patient will either go off chemotherapy or continue with doxorubicin and cyclophosphamide only.

In case of 2nd episode, reduce docetaxel dose from 60 to 50 mg/m². No further dose reduction is planned.
AC→T

Delay docetaxel treatment by maximum of two weeks.
As soon as patient recovers, treatment should continue with the following dose recommendations:
If patient recovers to Grade 1 toxicity, dose of docetaxel will be decreased from 100 to 75 mg/m^2. If patient not recovered to Grade 1 in two weeks, patient will go off chemotherapy.

In case of 2nd episode, reduce dose of docetaxel from 75 to 60 mg/m^2. 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.

5.3.2.6 Cutaneous reactions

Please refer to Appendix 13 for "skin" criteria.

Grade 0, 1, 2:

No change

Grade 3:

Delay until ≤ grade 1 for a maximum of two weeks. As soon as patient recovers, treatment should continue with the following dose recommendations:

For TAC: reduce dose of docetaxel from 75 to 60 mg/m^2. Second reduction of docetaxel allowed from 60 mg/m^2 to 50 mg/m^2.

For AC→T, reduce dose of docetaxel from 100 to 75 mg/m^2 for docetaxel. Second reduction allowed from 75 to 60 mg/m^2 for docetaxel.

If no recovery to ≤ grade 1 within two weeks delay, patient will go off chemotherapy.

5.3.2.7 Docetaxel Related 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 IV dexamethasone 10 mg (or equivalent) and IV diphenhydramine 50 mg (or equivalent). ♦ Resume docetaxel infusion after recovery of symptoms. ♦ At subsequent cycles, give IV dexamethasone 10 mg (or equivalent) and IV 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 IV dexamethasone 10 mg (or equivalent) and IV 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 IV dexamethasone 20 mg (or equivalent) and IV 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 IV 1 hour before docetaxel infusion. ♦ If a severe reaction recurs, patient will go off chemotherapy.
Anaphylaxis (NCI-CTC, v 2.0 grade 4 reaction)	NO FURTHER STUDY DRUG THERAPY

5.3.2.8 Docetaxel Related 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 that 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 indicated.

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.

5.3.2.9 Management of Cardiac Toxicity

Baseline measurements of LVEF 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 [50] criteria (< lower limit of normal for institution and decrease greater than 10% points compared to the LVEF at baseline).

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.

5.3.2.10 Other Toxic Effects

Other toxic effects should be managed symptomatically if possible.

- For grade 3 toxicities except anemia (see Appendix 13), 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.

5.4 Treatment Duration and Follow-up

5.4.1 Treatment Duration (Chemotherapy Only)

If a patient is randomized to the TAC arm, 6 cycles are to be administered.

If a patient is randomized to the AC→T arm, 4 cycles of AC followed by 4 cycles of single agent docetaxel should be administered.

In the event of breast cancer relapse or second primary malignancy (excluded are non-melanoma skin cancer, in situ carcinoma of the cervix and in-situ carcinoma of the breast (LCIS/DCIS) during treatment (see section 6.1 for efficacy definitions)), unacceptable toxicities or withdrawn consent, treatment should finish earlier.

5.4.2 End of Chemotherapy (EOC) Definition

End of chemotherapy (EOC) is defined as 21 to 28 days post the last infusion of chemotherapy.

Patients will be observed 3 to 4 weeks 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 hormonal therapy and/or radiotherapy...).

5.4.3 Follow-up Duration

Patients will be followed every 3 months for the first two years, every 6 months for years 3 – 5, and then once a year for ten years or until breast cancer relapse to document:

- Disease-free survival
- Survival
- Further therapy
- Quality of life (for the first two years only)
- Productivity and time loss (for the first two years only and in selected countries)
- Late side effects, including congestive heart failure. This will include chemotherapy, hormonal therapy and adjuvant radiotherapy related toxicities.
- 2nd primary malignancy

In case of administration of any systemic therapy (chemotherapy, hormonotherapy, genetherapy or immunotherapy) given for breast cancer relapse or 2nd primary malignancy (excluded are non-melanoma skin cancer, in situ carcinoma of the cervix and in-situ carcinoma of the breast (LCIS/DCIS) other than the agents outlined in the protocol, patients will be followed in an abbreviated follow-up for:

- Survival
- Congestive Heart Failure.

See Appendix 6 for the follow-up schedule. Abbreviated follow-up visits will be done yearly at the anniversary date of EOC until year 10 after EOC or until death.

5.4.4 Definition of First Follow-Up Visit (FUp1 and Fup1a)

Because of the difference in duration of treatments between the two arms, the first follow-up will be done as follows:

For the TAC Arm Only

FUp1a visit: An extra Follow-Up Visit 6 weeks after the EOC will be planned. The timing of this exam corresponds to the EOC visit in the AC→T arm. Quality of life, productivity and time loss (in selected countries) and physical exam must be performed.
FUP 1 visit: to be performed 4.5 months after the date of EOC visit.

For the AC->T arm:
FUP1 visit: will take place 3 months after the date of EOC visit

The addition of FUp1a visit in TAC arm is necessary in order to balance the timing of follow up assessments between the two arms.

5.5 Concomitant Treatment During Chemotherapy

Allowed:

1 G-CSF (in case of febrile neutropenia or infection or delayed neutrophil counts or primary prophylaxis at investigator discretion) (see sections 5.3.1.5 and 5.3.1)
2 Antiemetics (section 5.1.5)
3 Antiallergic measures (section 5.3.2.7)
4 Antibiotics
- oral prophylactic for TAC: oral prophylactic for AC→T if prior episode of severe infection
- IV 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 (untill relapse or up to 10 years).
2 Corticosteroids are not allowed, except as outlined in section 5.1.4 (premedication), sections 5.3.1 and 5.1.5 (antiemetic), and section 5.3.2.7) (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.
4 Concomitant treatment with amifostine (Ethyol®) will not be allowed during the course of active treatment with chemotherapy.
5 Concomitant treatment with Cardioprotectors (e.g. Dextrazoxane®) will not be allowed during the course of active treatment with chemotherapy.

5.6 Reasons for Discontinuation or Withdrawal From Chemotherapy

Reasons for premature withdrawal or discontinuation criteria include

1. Unacceptable Toxicity (see Section 5.2 Dose Modification).
2. Withdrawn Consent (see Informed Consent Appendix 7, page 6 of 7, Withdrawal From Study).
3. Breast cancer relapse, second primary malignancy (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix – see Exclusion Criteria 9a, 9b), death or administration of other

systemic cancer treatment other than study drug or hormonal therapy as per protocol (Section 5.4 Treatment Duration and Follow-up, Section 5.5 Concomitant treatment).

The reason and date of chemotherapy discontinuation for all patients will be documented on the case report form (e.g. 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.

Patients who stop chemotherapy for any reason OTHER THAN having been administered systemic anticancer therapy for disease relapse or 2nd primary malignancy (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix – see Exclusion Criteria 9a, 9b) must be followed in a regular follow-up.

5.7 Post Chemotherapy Treatment

5.7.1 Indication for hormonal therapy

Tamoxifen 20 mg p.o. daily for 5 years will be administered in either arm, 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. The estrogen and/or progesterone receptor determination will be done at the clinical site on the primary tumor. Results must be available prior to randomization.

Patients are allowed to switch to anastrozole in case of tamoxifen-related severe toxicities (e.g. hot flushes, vaginal bleeding, vaginal discharge, thromboembolic events). Anastrazole will be given at the dose of 1 mg daily. Of note, the total duration of the hormonal therapy, i.e. tamoxifen followed by anastrozole, should not exceed 5 years. Only post-menopausal patients are eligible to receive Anastrazole.

For post- menopausal women without contraindications to the use of Tamoxifen, a sequential therapy is allowed, consisting of Tamoxifen for 2 to 3 years followed by Anastrozole or Exemestane for a maximum of 5 years of hormonal therapy.

Post- menopausal patients who have completed 5 years Tamoxifen are allowed to continue the hormonal treatment with letrozole for a maximum of 3 years

Note: - The use of AIs should be accurately documented and reported on page FU4 of the CRF,

- The same approach is followed for all patients treated in the BCIRG 005/TAX GMA 301 study in order to avoid treatment imbalance between the 2 arms.

- Each center will be requested to provide BCIRG data center with their institution guideline related to the use of aromatase inhibitor by completing a questionnaire.

In case of breast cancer relapse and/or further systemic chemotherapy, hormonal-therapy treatment should be discontinued. Hormonal therapy following a secondary primary malignancy will be continued at the discretion of the investigator.

5.7.2 Radiation Indication

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. Each patient's type and dose of radiation therapy will be documented in the CRF.

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. Boost radiation therapy will be left at the discretion of the investigator. This will be done in a consistent manner according to the guidelines at each institution. Postoperative radiation guidelines specific to each institution will be collected by BCIRG. Each patient's type and dose of radiation therapy will be documented in the CRF.

5.7.3 Therapy after protocol treatment is discontinued

If patients are removed from therapy because of breast cancer relapse, further treatment is at the discretion of the investigator. The metastatic regimen(s) used will be collected in the Case Report Form.

Except for study hormonotherapy and radiotherapy as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) after completion of the chemotherapy and before tumor relapse is documented. If this is not possible, the patient will be considered as censored at the date of initiation of new antitumor therapy and will be analyzed as failure for the calculation of disease free survival.

5.8 Study Evaluations

5.8.1 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/vital signs.	14 days
3 Hematology **	Hemoglobin WBC and neutrophil count Platelet count	14 days

4 Biochemistry **	Liver function: • Alkaline phosphatase, • ASAT (SGOT), ALAT (SGPT), • Bilirubin Renal function: • serum creatinine, • creatinine clearance (if indicated) Menopausal Status For patients ≤ 55 years old and having had a hysterectomy without bilateral ovariectomy • FSH ~~a)~~• LH	14 days Liver function tests are to be repeated within 3 days, if abnormal results. 3 months
5 HER2neu Assessment	Negative FISH test (BCIRG central lab confirmation)	Prerandomization
6 ER/PR status	√	Prerandomization
7 Pregnancy test	urine or serum (if applicable)	7 days
8 Imaging***	mandatory for all patients: • Contralateral mammography • chest-X-Ray (PA and lateral) and/or CT and/or MRI • abdominal ultrasound and/or CT scan and/or MRI • bone scan, and bone X-ray in case of hot spots in bone scan Other instrumental examinations as indicated.	3 months
9 ECG	ECG	3 months
10 LVEF	MUGA scan or echocardiography	3 months
11 Quality of life	QLQ-C30, BR23 & Euroquol (EQ-5D) questionnaires (see Appendix 10).	14 days
12 Socio-economy	Productivity and time loss questionnaire (see Appendix 11).	14 days
13 Other Investigations	As clinically indicated.	3 months
14 Existing signs and symptoms	Baseline evaluation to document existing symptoms.	14 days
* Informed Consent should be obtained prior to any tests specified in this clinical protocol that are not part of the patient's routine care ** Laboratory assessments will be performed whenever possible by the same laboratory throughout the study. ** Every effort will be made to use the same instrumental examination from baseline through follow-up.		

5.8.2 Study Entry - Registration

All eligible patients must be registered with the coordinators of the study based in Paris, for all the countries outside Canada and USA, or Los Angeles, for all Canadian and US centers, 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 the coordinators of the study. A registration package outlining the exact process for registering a patient and the registration forms will be forwarded and reviewed to all sites at the initiation site visit, by the site CRA.

[redacted] for all countries outside Canada and USA

[redacted] for Canada and USA

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 Investigator's name

4 Patients' identification (first letter of the first name, first letter of the middle name [if not applicable record -] and the first letter of the last name)

5 Patient's birth date (day/month/year)

6 Performance status

7 Date treatment planned.

8 Verification of selected inclusion and exclusion criteria as identified in the patient registration form.

9 Date when the paraffin block was sent to the designated BCIRG laboratory for HER2neu testing. Her2neu screening will be performed by regional BCIRG designated central laboratories. The result of the test will be sent directly from the labs to the BCIRG Study Registration Officer, who will determine patient eligibility based on the registration form received from the clinical site and from the result of the HER2neu test, received from the designated lab. See Appendix 3 for more details on the process.

Each eligible patient will be randomized according to a center specific randomization block to receive either docetaxel, doxorubicin and cyclophosphamide (TAC) or doxorubicin and cyclophosphamide followed by docetaxel (AC→T).

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.

Note 1: Interval between definitive surgery that includes axillary lymph node dissection and registration is less than 60 days.

Note 2: If further tests or results are needed to be performed at the time of registration, we will allow 5 working days from the time of registration to the time of randomization. Treatment must start within 8 days from the time of randomization.

5.8.3 Evaluation During Chemotherapy

All patients during the study must be evaluated according to the schedule outlined in Appendix 5 until they are 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, QLQ BR23, Euroquol (EQ-5D) questionnaires	See Section VII
7 Socio-economy	Productivity and time loss questionnaire	See section VIII
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 version 2.0 (Appendix 13). In case NCI-CTC version 2.0 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. Every effort will be made to use the instrumental examination from baseline through follow-up.		

5.8.4 Evaluation at End of Chemotherapy

(See Section 5.4.2 End Of Chemotherapy definition). This visit will be performed 21-28 days after the last treatment as summarized in Appendix 5: work-up will include = physical examination, hematology, biochemistry, record of toxicity, socio-economy and quality of life. All evaluations for the End of Chemotherapy will be captured in the last cycle in the case report form.

5.9 Evaluation in Follow-up After End of Chemotherapy

Timing of follow-up visits is based on the end of chemotherapy (EOC) and will be performed according to the following schedule (see section 5.4.2 End of Chemotherapy definition, Section 5.4.4 Definition of First Follow-up Visit and Appendix 6). Clinical follow-up may be more frequent according to the standard of practice at the participating center.

Note: For the TAC Arm Only

"FUp1a" visit: an extra Follow-Up Visit 6 weeks after the EOC will be planned. The timing of this exam corresponds to the EOC visit in the AC→T arm. Quality of life, Productivity and time loss (in selected countries) and physical exam must be performed.

Both Arms

First 2 years	every 3 months	physical examination
	every 6 months	physical examination
	every 12 months	physical examination and mammography
	at 6, 12 and 24 months	quality of life and productivity and time loss (in selected countries) questionnaires
Years 3 to 5	every 6 months	physical examination
	every 12 months	physical examination and mammography
Years 6 to 10	every 12 months	physical examination and mammography

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

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 hormonal therapy and/or radiotherapy...).

In case of administration of any systemic therapy (chemotherapy, hormonotherapy, genetherapy or immunotherapy) given for breast cancer relapse or 2nd primary malignancy (excluded are non-melanoma skin cancer, in situ carcinoma of the cervix and in-situ carcinoma of the breast (LCIS/DCIS) other than the agents outlined in the protocol, patients will be followed in an abbreviated follow-up for:

- Survival
- Congestive Heart Failure.

See Appendix 6 for the follow-up schedule. Abbreviated follow-up visits will be done yearly at the anniversary date of EOC until year 10 after EOC or until death.

VI SAFETY AND EFFICACY PARAMETERS

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 (note: routine blood pressure, heart rate, temperature will not be captured in the CRF), 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) as per protocol. The same method of LVEF assessment must be used throughout the study. We strongly advise that all echocardiography or MUGAs be determined at the same radiology facility used at baseline.

- Imaging studies as per protocol

- Adverse events: each patient will be assessed regularly for potential adverse events according to the NCI Common Toxicity Criteria, version 2.0 (Appendix 13).

Toxicities which cannot be graded using the NCI Common Toxicity Criteria, Version 2.0 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 platelet count, hemoglobin

- *Biochemistry*: total bilirubin, alkaline phosphatase, SGOT (ASAT), SGPT (ALAT) creatinine, creatinine clearance (as indicated)

- *Pregnancy test*: urine or serum (if applicable)

i)• *Menopausal Status*: for patients ≤ 55 years of age and having had a hysterectomy without bilateral ovariectomy, FSH and LH will need to be performed (test to be performed within 3 months of registration).

ii)• *Hormonal Receptor Status (estrogen and/or progesterone receptor status)*: results must be known prior to randomization.

- *HER2neu determination (FISH):* results must be known prior to randomization

6.2 Efficacy Evaluations

All randomized patients will be included in an intent-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 in the appropriate follow-up forms in the CRF.

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 Pathology Laboratory (Los Angeles or Basel, depending on the countries) for confirmation of primary or metastatic status along with pathologic and molecular studies. At the site initiation visit, a package outlining the process for shipping to the BCIRG Central Pathology Lab will be presented.

6.2.1.4 Other circumstances

The following do not constitute relapse, 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 breast cancer 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.

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 breast cancer relapse, second primary cancer (with the exception of curatively treated non-melanoma skin cancer or carcinoma in situ of the cervix – see Exclusion Criteria 9a, 9b), 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

A comparison of quality of life between the two arms is a secondary endpoint of the study. Centers participating in the analysis will be defined prior to initiation of the study at their center. Some countries may not participate due to the questionnaires not being available in the patient's first language.

The EORTC cancer-specific and Euroquol (EQ-5D) general health indexes were chosen in this comparative study.

The QLQ-30 (v.3.0) profile questionnaire and the BR-23 module specific to breast cancer are, respectively, 30 and 23 items in a questionnaire format. The Euroquol (EQ-5D) is a five questions format in addition to a visual analog scale. They will be self-administered by the patient (Appendix 10) and should be completed in accordance with the following schedules.

	AC→T	TAC
Baseline	Within 14 days prior to randomization	Within 14 days prior to randomization
Cycle 4	day –1 to day 1 (before chemotherapy)	day –1 to day 1 (before chemotherapy)
Cycle 7 AC→T EOC* TAC	day –1 to day 1 (before chemotherapy)	EOC* Visit
EOC* AC→T Fup1a TAC♦	EOC* Visit	6 weeks after the EOC visit Fup1a visit
Follow-Up	Follow-up Visit at 6, 12 and 24 months after EOC	Follow-up visit at 7.5, 13.5, 25.5 months after EOC* visit
At Relapse	At Relapse Visit	At Relapse Visit

* EOC is the End of Chemotherapy Visit (3 or 4 weeks post last infusion of chemotherapy – See Section 5.4.2 End of Chemotherapy Definition)

♦ Fup1a visit is an extra visit planned for the TAC arm 7 weeks after EOC. This corresponds to the EOC visit in the AC→T arm.

This schedule has been established to best assess potential differences in the longitudinal effects on quality of life and other socio-economic parameters between the two arms, particularly given the different lengths of treatment with each regimen. The patient should complete the questionnaires by herself at the center prior to physician assessment and prior to receiving treatment.

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

VIII SOCIO-ECONOMIC EVALUATION

A socio-economic comparison between the two arms will be also performed. This productivity and time loss questionnaire will only be given and analysed in selected countries (ie. Canada, Germany and USA). The productivity and time loss questionnaires will be self-administered by the patient (see Appendix 11) and should be completed in accordance with the following schedules.

	AC→T	TAC
Baseline	Within 14 days prior to randomization	Within 14 days prior to randomization
Cycle 4	day –1 to day 1 (before chemotherapy)	day –1 to day 1 (before chemotherapy)
Cycle 7 AC→T EOC* TAC	day –1 to day 1 (before chemotherapy)	EOC* Visit
EOC* AC→T Fup1a TAC♦	EOC* Visit	6 weeks after the EOC visit Fup1a visit
Follow-Up	Follow-up Visit at 6, 12 and 24 months after EOC	Follow-up visit at 7.5, 13.5, 25.5 months after EOC* visit
At Relapse	At Relapse Visit	At Relapse Visit

* EOC is the End of Chemotherapy Visit (3 or 4 weeks post last infusion of chemotherapy – See Section 5.4.2 End of Chemotherapy Definition)

♦ Fup1a visit is an extra visit planned for the TAC arm 6 weeks after EOC. This corresponds to the EOC visit in the AC→T arm.

This schedule has been established to best assess potential differences in the longitudinal effects on socio-economic parameters between the two arms, particularly given the different lengths of treatment with each regimen. The patient should complete the questionnaire by herself at the center prior to physician assessment and prior to receiving treatment.

It is recommended that a key person (e.g. a 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.

IX DATA ANALYSIS / STATISTICAL CONSIDERATIONS

9.1 Sample Size Determination

The sample size determination was done based on the following assumptions:
The primary objective of this trial is to show that TAC differs from AC→T in terms of disease-free survival (DFS). The following assumptions are made:

- The DFS at 5 years of node-positive patients receiving AC→T is around 50%.
- It is of clinical interest to detect a 5% improvement in 5-year DFS (i.e. an increase from 50% to 55%).
- The error rate for a false positive outcome (α) is set to 5%, using two-sided significance tests.
- The error rate for a false negative outcome (β) is set to 20%, i.e. the power of the trial is set to 80% for the difference of clinical interest.

A sample of 3,034 eligible patients is required under these assumptions [51]. Assuming further that about 3% of the patients will be found ineligible after randomization, the total sample size needed in the trial is 3,130 (1,565 patients per treatment arm).

Updated data on DFS from BCIRG 001 study (TAC Arm) have been used to determine the number of events required for the interim and main Analyses by keeping a power of 80% and α =0.05 as originally planned.

[redacted]

[redacted]

[redacted] he randomization is also stratified for center (see section 9.3.3) and for estrogen receptor status (positive versus negative) and for progesterone receptor status (positive versus negative).

9.2 Randomization

The treatment assignment will be based on a dynamic minimization procedure using center, number of axillary lymph nodes involved (N1-3 versus N4+), hormonal receptor status status (estrogen and/or progesterone receptor positive versus negative), as factors in the minimization algorithm, which will use a stochastic treatment allocation algorithm based on the variance method [52].

9.3 Efficacy Evaluation

9.3.1 Efficacy Parameters

Primary

The primary efficacy parameter will be Disease-Free Survival (DFS). The DFS is defined as the interval from the date of randomization to the date of local, regional or metastatic Breast cancer relapse or the date of second primary cancer or death from any cause, whichever occurs first.

Secondary

Secondary efficacy parameters will be Overall Survival (OS) and quality of life.

9.3.2 Populations To Be Analyzed

The primary efficacy analysis will be performed on the Intent-to-Treat (ITT) population, defined as the population of all randomized patients analyzed in the treatment arm they were assigned to. Randomized patients who did not receive chemotherapy will be analyzed in their group of randomization. The analysis of DFS and OS will also be performed on the eligible patients population, defined as the ITT population patients less patients who were randomized but were clearly not eligible for the trial.

9.3.3 Statistical Methods

The Kaplan-Meier product limit method will be used to estimate the DFS and the OS. The logrank test, stratified for the number of axillary lymph nodes involved (N1-3 versus N4+), for ER status (negative versus positive), and for PR status (negative versus positive) will be used to compare the two treatment arms with respect to DFS and OS. All tests of hypotheses will be two-sided. Confidence intervals of the median survival will be calculated using the method of Simon [53].

Cox's proportional hazards regression analysis will be performed for DFS and OS in order to adjust the treatment comparison for the major prognostic factors. These factors include age, menopausal status, type of surgery, histopathological findings, tumor size, pathological markers and molecular markers. Such adjusted analyses will be considered secondary to the main analysis. Any subset analyses, for instance by number of axillary lymph nodes involved (N1-3 versus N4+), will be reported with appropriate caveats.

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. Therefore, it is not planned to include any center effect in the analyses. However, should there be centers with a large recruitment, 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.

9.3.4 Interim Analyses, Main Analysis and Follow-Up Analyses

One interim efficacy analysis will be performed after 50% of the expected events have been observed (344 events). The O'Brien-Fleming spending function will be used with a significance level of 0.003 for the interim analysis. This allows the use of a significance level of 0.049 for the main analysis.

A total of 688 events are required among all patients at the time of the main analysis.

Some patients are expected to have a very long disease free survival. Consequently, a 10-year clinical follow-up has been planned. Two confirmatory analyses will be performed at 3 years and 5 years after the main analysis. The purpose of these follow-up analyses is to update the DFS and OS estimates. All randomized patients will be followed until death or up to 5 years after the main analysis whichever occur first.

Except in the case of overwhelming interim results, the recommendation to use TAC or AC→T in the target patients' population will be given after the main analysis (5-year analysis) at the discretion of the Steering Committee.

9.4 Safety Evaluation

9.4.1 Grading Of Adverse Events

The National Cancer Institute Common Toxicity Criteria, version 2.0 (NCI-CTC, v 2.0) 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, v 2.0 a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, and 4: life threatening.

9.4.2 Populations To Be Analyzed

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

9.4.3 Statistical Methods

Adverse events will be compared using a two-tailed χ^2 tests or, when expected counts are low, Fisher's exact test or one of its generalizations. 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.

Descriptive statistics will be given on the number of patients in whom the study medication had to be reduced, delayed or permanently stopped.

9.5 Independent Data Monitoring Committee

9.5.1 Composition And Mission Of The IDMC

In addition to the Steering Committee, an Independent Data Monitoring Committee (IDMC) will be set up. It will be composed of at least three 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 IDMC 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 monitors the progress of the trial. The IDMC will be responsible for review of the trial's efficacy and safety data.

9.5.2 Meetings Of The IDMC

In the absence of any major event requiring the meeting of the IDMC members, an annual meeting of the IDMC will be held. The committee will meet annually to assess the incidence and severity of each serious adverse event and adverse event. In the case where an unanticipated serious event or incidence is reported prior to the scheduled meeting, a meeting will be called immediately to address and assure the safety of the patients in the study. The latter may also include data that has come in from other studies but involves the same agents being administered in this study. The latter may also include newly presented efficacy data from another relevant study whose data in some way may influence the current BCIRG 005 study. The IDMC will have written operating procedures and will maintain records of all its meetings.

9.5.3 Documentation Provided To The IDMC

Before any meeting of the IDMC, the Data Center should provide the IDMC 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 arm and participating institution (whenever necessary). In addition, the Data Center will provide the IDMC with efficacy data at the time of the interim analysis. All results are confidential and must not be divulged to nonmembers of the IDMC.

9.5.4 Recommendations Of The IDMC

After each meeting, the IDMC will provide the Steering Committee with a written recommendation to either modify the trial (with reasons), or discontinue the trial (with reasons), or make the interim results of the trial public (with reasons), or continue the trial unchanged. The final decision to amend the protocol or to discontinue the trial will be taken only by the Steering Committee.

X ADVERSE EVENTS / TOXICITY

10.1 Definitions

10.1.1 Adverse event

The term adverse event covers any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the well being of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

The adverse event may be:

- A new illness
- Worsening of a concomitant illness
- An effect of the study medication, including comparator
- A combination of two or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term “adverse event”.

Adverse events fall into the categories “non serious” and “serious” (see Section 10.1.2 Serious adverse event).

Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event. Planned surgical measures permitted by the clinical study protocol and the condition(s) leading to these measures are not adverse events.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters and should only be recorded as an Adverse Event if the outcome is serious (see section 10.1.2 Serious adverse event).

10.1.2 Serious adverse event

A serious adverse event is one that at any dose:

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity[2]
- Is a congenital anomaly/birth defect
- Is an important medical event[3]

[1]“Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]“Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.

[3] Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes

listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The List of Critical Terms (1998 adaptation of WHO Adverse Reaction Terminology Critical Terms List) should be used as guidance for adverse events that may be considered serious because they are medically important. (The List of Critical Terms can be found in the "Instructions for reporting serious adverse events (SAEs) occurring in clinical trials".

Cases of overdose with an adverse event that meets one of the criteria given above should of course be reported as "serious".

Clarification of the difference in meaning between "severe" and "serious":
The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on the outcome or action criteria usually associated with events that pose a threat to life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Severity of the adverse events should be graded according to the NCI Common Toxicity Criteria, version 2.0 (see Appendix 13).

10.1.3 Alert terms and other reasons for expedited reporting to Pharmacovigilance.

No special events are subject to reporting as alert terms in this study.

Cases in which a "significant overdose" was taken and a non-serious adverse event or no adverse event occurred are to be reported to the sponsor in an expedited manner on a serious adverse event form, "Serious Adverse Event/Expedited Report from a Clinical Trial" form.

A "significant overdose" includes any overdose in which either a serious adverse event, a non-serious adverse event, or no adverse event occurs and is considered by the investigator as clinically relevant, i.e. poses an actual or potential risk to the subject's well being.

10.2 Period of observation

For the purposes of this study, the period of observation for collection of Adverse Events extends from the time the subject starts treatment with the study medication until 30 days after the last infusion of chemotherapy.

If the investigator detects a serious adverse event in a study subject after the end of the period of observation, he or she should contact the sponsor - via the BCIRG Safety Manager - to determine how the adverse event should be documented and reported. For a definition of study medications see Section 5.1. As a general guide: late fatal complications or delayed toxicities of medical importance like CHF, if considered related to prior study medications, should be documented and reported as a serious adverse event.

During the period of observation, cancer relapse (defined as component of the clinical efficacy endpoint) will not be reported as serious adverse event unless it satisfies the Serious Adverse Event definition (refer to section 10.1.2). After the end of the observation period, cancer relapse will not be reported as a serious adverse event.

Second primary malignancies, that satisfy the Serious Adverse Event definition (refer to section 10.1.2) will be reported as a serious adverse event regardless of causality and regardless of time of occurrence (during or after the period of observation).

Death from any cause that satisfy the Serious Adverse Event definition (refer to section 10.1.2) will be reported as a serious adverse event during the observation period. They will not be reported as a serious adverse event after the observational period unless they are study drug related.

10.3 Documentation and reporting of adverse events by investigator

All adverse events that occur after the start of the observation period set in this protocol (see Section 10.2 - Period of observation) must be documented on the pages provided in the case report form in accordance with the "Instructions for the completion of adverse event reports in clinical studies". These instructions are provided in the investigator's study file and in the case report form itself.

The following approach will be taken for documentation:

- All adverse events (whether serious or non serious, or considered as an alert term) must be documented on the "Adverse event" page of the case report form.
- If the adverse event is serious (see Section 10.1.2 - Serious adverse event), the investigator must complete, in addition to the "Adverse Event" page in the case report form, a **"**Serious adverse event/ Expedited report from a clinical trial" form at the time the serious adverse event is detected. This form will be sent to the sponsor's representative:

For all countries outside Canada and USA

BCIRG Safety Manager

[redacted]

For Canada and USA

[redacted]

who will; forward it to Aventis.

- In the situation when a "significant overdose" had occurred without any adverse event (see Section 10.1.3 -Alert terms and other reasons for expedited reporting to Pharmacovigilance), the investigator should only complete a **"**Serious adverse event/ Expedited report from a clinical trial" form. This form must be sent to the sponsor's representative – BCIRG Safety Manager. In this situation, there is no need to complete the "Adverse event" page in the case report form.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If appropriate, component symptoms should also be listed below the diagnosis. If only non-specific signs or symptoms are present, then these should be recorded as a diagnosis.

All subjects who have adverse events, whether considered associated with the use of the study medication or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up. Should the adverse event result in death, a full pathologist's report should be supplied, if possible.

All questions on the completion and supply of adverse event report forms and any further forms issued to the investigator at a later date to clarify unresolved issues should be addressed to the sponsor's representative – the BCIRG Safety Manager.

10.4 Immediate reporting to BCIRG

Serious adverse events and adverse events that fulfill a reason for expedited reporting to Pharmacovigilance (alert term and/or "significant overdose", as defined in Section 10.1.3 - Alert terms and other reasons for expedited reporting to Pharmacovigilance) must be documented on a "Serious adverse event/ Expedited report from a clinical trial" form (see Appendix 8) in accordance with the "Instructions for reporting serious adverse events (SAEs) occurring in clinical trials". This form must be completed and supplied to BCIRG's Safety Manager within 24 hours, or at the latest on the following working day. The "Serious adverse event/ Expedited report from a clinical trial" form is also provided in the investigator's study file together with the instructions to fill out such forms.

The BCIRG Safety Manager will then report the adverse events to the sponsor (Aventis) as provided for in the Agreement for Clinical Research Management Services between the sponsor, Aventis and BCIRG. The Sponsor will then report the adverse events to the responsible health authorities in compliance to all legal and reporting requirements and as provided for in aforementioned Agreement.

The sponsor will ensure that all legal reporting requirements are met.

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study medication.

Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up "Serious adverse event/ Expedited report from a clinical trial" form.

The "Instructions for the completion of adverse event reports in clinical studies" give more detailed guidance on the reporting of serious adverse events, adverse events that comply with alert terms, and adverse events initially reported as non serious that become serious. In the latter situation, when a non-serious event becomes serious, details must be forwarded immediately to the sponsor's representative – the BCIRG Safety Manager on a "Serious adverse event in a clinical trial" form.

XI STUDY MEDICATION

11.1 Drug Packaging, Labeling, Dispensing and Storage

Docetaxel will be supplied by Aventis.

11.1.1 Packaging and Labeling

DOCETAXEL (see Appendix 9 for detailed information)

Packaging:

Docetaxel will be provided as a sterile concentrate for infusion (concentration = 40 mg/mL).
The appropriate solvent for diluting the docetaxel concentrate for infusion will also be provided.
Vials are intended for single administration only.

Labeling:

The label attached to the Taxotere® (docetaxel) will contain the following information:

- Manufacturer's name and address
- Sponsor's name and address
- Product name
- Study code number
- Contents
- Directions for Use

Storage Conditions
Batch number and packaging numbers
Legal requirements

11.1.2 Administration to Patients

Handling precautions:

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

11.1.2.1 Docetaxel (see Appendix 9)

For preparation of the docetaxel solution, please refer to Appendix 9.

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

11.1.2.2 Doxorubicin

See preparation instructions on the package insert.

11.1.2.3 Cyclophosphamide

See preparation instructions on the package insert.

11.1.3 Storage (see Appendix 9)

All drug supplies must be kept in an appropriate locked room that 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 9.

For the vials of doxorubicin, cyclophosphamide: see storage instructions on the package insert

11.2 Drug Accountability

The person responsible for drug dispensing is required to maintain adequate records of all study drugs (docetaxel, doxorubicin and cyclophosphamide). These records (e.g. drug movement form) include the dates the study medications are received from the manufacturer (if applicable), the dates dispensed for the individual patient and the dates destroyed at the site as per each country's policy and guidelines (or returned to manufacturer). Patient number, date of infusion, investigator name, lot number, expiry date of the study medication must be documented 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.

XII ADMINISTRATIVE ASPECTS

12.1 Monitoring, Auditing, and Inspecting

The study will be monitored by regular site visits and telephone calls to the investigator by members of the BCIRG 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 BCIRG and/or Aventis may conduct site audits. The investigator will provide direct access to source data/documents for trial related monitoring, audits, IRB/EC review and regulatory inspections.

12.2 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.

12.3 Recording of Data

The study will be conducted using paper based CRFs. NCR™ Case Report Forms will be supplied by BCIRG providing a white original and colored copies. These forms must be typewritten or ***PRINTED LEGIBLY*** using black ballpoint pen when prepared for submission to BCIRG.

The forms should be verified against all original records (and workbooks, if applicable) by the BCIRG. Clinical Monitor before submission. The bottom copy will be retained in the investigator's files, and all other copies will be returned to the BCIRG central operational office in Edmonton Canada. No case report forms are to be mailed to the BCIRG 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. “Relationship to medication” during the study chemotherapy, “most likely cause” during the follow-up, socio-economic data as “employment status”, “productivity and time loss” and answers to QOL questionnaires will be considered to be source data.”Relationship to medication” during the study chemotherapy, “most likely cause” during the follow-up, socio-economic data as “employment status”, “productivity and time loss” and answers to QOL questionnaires will be considered to be source data.

12.4 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 BCIRG for all required study documents.

12.5 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, BCIRG, or Aventis 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.

12.6 Patient Informed Consent (Appendix 7)

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.

12.7 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 BCIRG and Aventis.

Particular attention is drawn to the FDA's regulation regarding the IRBs. By signing the "Statement of Investigator" form (Form 1572), the investigator provides BCIRG and Aventis 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 Aventis) 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.

12.8 Declaration of Helsinki

This study is to be performed in accordance with the Declaration of Helsinki (Edinburgh 2000 Amendment), as described in Appendix 1.

12.9 Insurance of Liabilities

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

12.10 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 BCIRG and Aventis, 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 BCIRG and Aventis and will be documented in a memorandum. The Ethics Committee/IRB may be notified of administrative changes at the discretion of BCIRG.

12.11 Use of Information and Publication

All information concerning the study drug supplied by Aventis 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, BCIRG technical methodology, and basic scientific data. This confidential information shall remain the sole property of BCIRG and Aventis, shall not be disclosed to others without prior written consent from BCIRG and Aventis and shall not be used except in the performance of this study.

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 BCIRG and Aventis with complete test results and all data developed in this study. Only BCIRG and Aventis 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 BCIRG. BCIRG and Aventis 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 BCIRG and Aventis. Interim abstracts will be presented according to the statistical plan and in agreement with BCIRG and Aventis .

In the event BCIRG and Aventis choose to publish the data from this study, BCIRG and Aventis 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.

XIII INVESTIGATOR'S AGREEMENT

I have read the preceding protocol

BCIRG 005
TAX GMA 301

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS DOXORUBICIN AND CYCLOPHOSPHAMIDE FOLLOWED BY DOCETAXEL (AC→T) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER HER2NEU NEGATIVE PATIENTS WITH POSITIVE AXILLARY LYMPH NODES. BCIRG 005

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 March 2003. I will provide copies of the protocol and all drug information relating to preclinical and prior clinical experience furnished to me by Aventis, 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

_____
Global Project and Medical Director BCIRG Date

_____
Medical Director, GMA Aventis Date

XIV REFERENCES

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APPENDIX 1 - DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly
Helsinki, Finland, June 1964
and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. 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."

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

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate 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.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical 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 consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

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

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best-proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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 – CENTRAL LAB PROCEDURE

Protocol for BCIRG Designated Central Laboratories

A. HER2neu FISH Testing

Human Epidermal Growth Factor Receptor 2 (HER2)

Abnormal expression of human epidermal growth factor receptor 2 (HER2) is frequently observed in a number of primary tumors, suggesting that the over expression of this growth factor receptor may contribute to transformation and tumorigenesis. In most cases, HER2neu protein over expression is thought to result from gene amplification and has been correlated with poor clinical outcome in patients with breast and ovarian cancers that over express HER2neu. Approximately 25% to 30% of patients with breast and ovarian cancers over express HER2neu.

The BCIRG 005 study requires, as one of the patient eligibility criteria, HER2neu NON amplification which represents 2/3 of the breast cancer patient population. Approximately 4,163 patients are expected to be screened in order to identify 3, 130 patients whose breast cancer does not amplify the HER2neu gene.

A representative paraffin block from potentially eligible women with breast cancer will be tested for c-erbB-2 status using Fluorescence In-Situ Hybridization (Vysis kit) in one of the BCIRG designated central laboratories.

[redacted] U.S.A. will be responsible for the HER2neu screening procedure. The two BCIRG central laboratories are as follows:

For Sites in North, South America, Asia, Australia

[redacted]
USA

For All Other Countries

[redacted]
Switzerland

Procedure:

All patients identified by the participating center as potentially eligible will start the study screening procedures as per study protocol.

A representative tumor block will be sent by the clinical site to one of the BCIRG designated labs. The block will be sent accompanied by a HER2neu screening form provided by BCIRG to the clinical site. This form will include a patient identifier such as patient initials, patient's date of birth and clinical site number.

The BCIRG laboratories will perform the *c-erb*B-2 analysis using the Vysis FISH kit and report the result to the BCIRG Registration Officer. The lab will then be informed by the Registration Officer if the patient was eligible and will either send the block back to the originating centre (if patient is not accrued to a BCIRG trial) or to the BCIRG designated Central Pathology laboratory (if the patient is accrued to the BCIRG trial). See Appendix 3'.

Operating Principles for the BCIRG Designated Labs:

1. Use of the Vysis kit.
2. Quality control and standardized procedure as determined by [redacted].

~~B.~~3. Turn-around time of 5 working days for faxing results to the BCIRG Registration Officer.

4. The disposal procedure for the blocks is as follows:

1. - all cases not accrued to a BCIRG trial (as informed by the BCIRG Registration Officer) should have their blocks returned directly to the contributing centre.

2. - all cases enrolled post HER2neu screening for BCIRG trials will have their blocks forwarded to the BCIRG designated Central Pathology Laboratory for molecular studies

C.B. Pathology and Marker Review

The purpose of this investigation is to establish the baseline characteristics of the tumors and ensure comparability between the experimental arms. Each tumor will be tested for:

i. a number of accepted histo-pathologic and molecular marker prognostic factors and

ii. several other factors with proven utility in predicting response to Taxotere®.

Due to the well described difficulty in obtaining inter-observer reproducibility in the assessment of pathologic factors, the assessments of these prognostic and predictive factors will be performed by a central lab.

Methodology

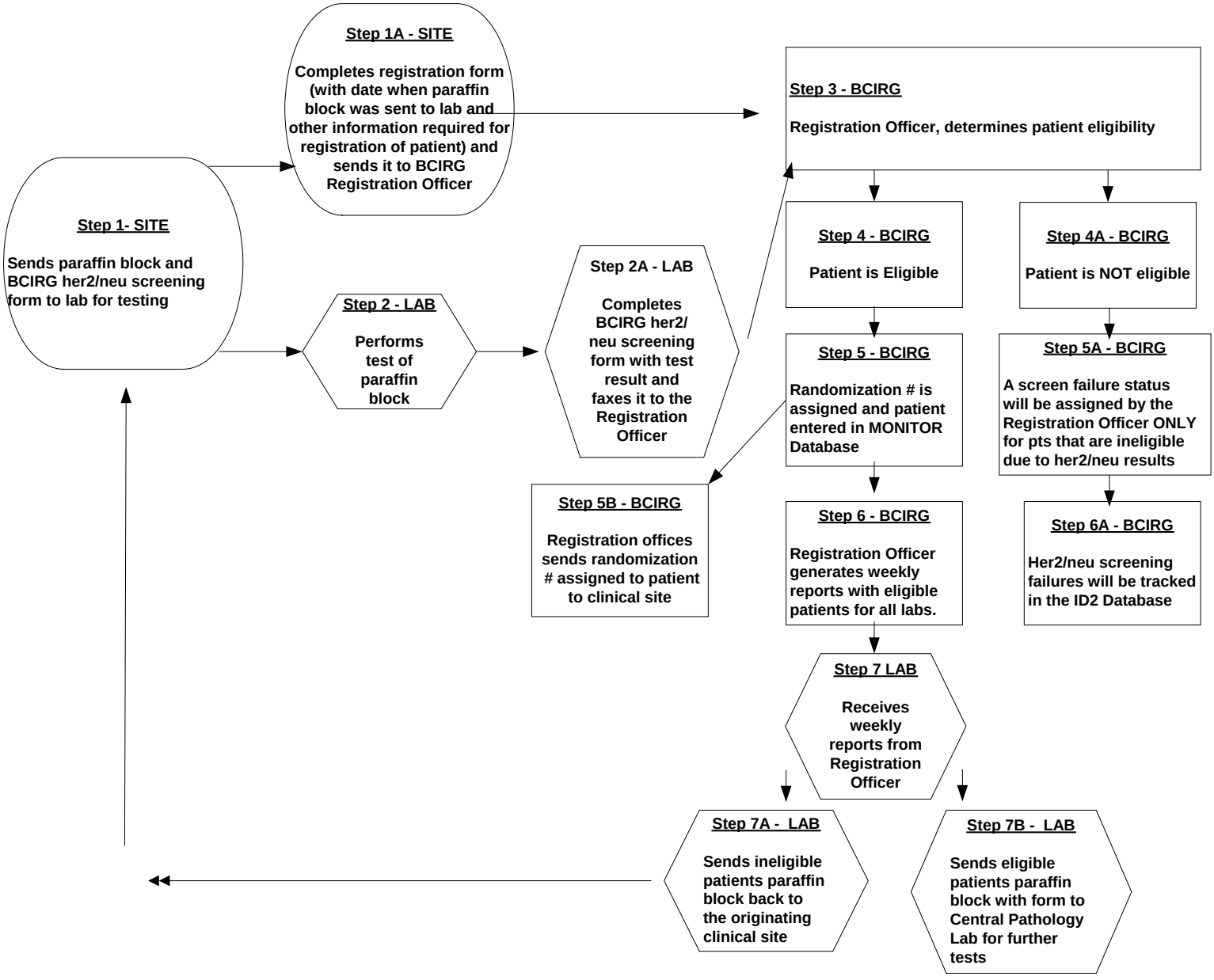
Hematoxylin and Eosin stained slides prepared from the paraffin block submitted for FISH testing will be assessed for histologic subtype, grade and vascular invasion. Additional unstained slides from the same block will be assayed for *ER, PR, p53* and *MIB-1* using automated immunohistochemistry at the BCIRG designated Central Pathology Laboratory. Histopathologic and immunohistochemical assessment of these factors will be performed by a single reference pathologist with external review of 30% of the material by a second observer. If indicated, the investigation of the *Bcl* family (Bcl-2, bax, Bcl-X and Bag-1) will be done in collaboration with [redacted] MD, Ph.D., [redacted] If indicated, the investigation of the tubulin isoforms (II, III, IV and Tau) will be done in collaboration with [redacted] France. If indicated, the investigation of MUC1 will also be performed at the Central Pathology Laboratory.

The pathology materials which must be supplied are:

1. one paraffin block from a representative area of the tumor. If insufficient material remains in this original block, the center will be contacted for an alternate block. 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 may be returned to the original pathology lab at the close of the trial if desired so by the patient. Blocks will otherwise be stored in a tumour bank for future investigations.
2. a copy of the pathology report for the specimen from which the block in part I is derived.

APPENDIX 3' FLOW CHART OF HER2/NEU SCREENING AND CENTRAL PATHOLOGY

BCIRG her2/neu Flowchart



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		DURING THERAPY	End of Chemo-therapy ****	Follow-up*****
	completed no more than (time) prior to registration		Every 3 weeks		
Patient informed consent	before study entry	X			
History	14 days	X			
Physical examination Weight Performance Status	14 days	X	X*	X	
Signs and symptoms**	14 days	X	X	X	
Adverse events			X	X	
Concomitant medication***	14 days	X	X	X	
Hematology Hemoglobin, WBC, neutrophils, platelets	14 days	X	X[1]	X	
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	
Renal function creatinine creatinine clearance (if indicated)	14 days	X	X		
Menopausal Status For women ≤ 55 years of age and having had hysterectomy without bilateral ovariectomy FSH LH	3 months	X			
FISH TEST (negative)	before study entry				
ER Status / PR Status	before study entry				
Pregnancy test (urine or serum)	7 days	X			
ECG	3 months	X	as clinically indicated		
LVEF MUGA scan or echocardiography	3 months	X	as clinically indicated		
Mammography	3 months	X			
Work up to rule out metastatic disease					
chest-X-ray (PA and lateral) and/or chest CT scan and/or chest MRI	3 months	X			
abdominal ultrasound and/or CT and/or MRI	3 months	X			
bone scan and bone X-ray in case of hot spots in bone scan	3 months	X			
Quality ofLife	14 days	X	X	X	X
Other investigations	as clinically indicated				

X[1] CBC and differential is to be done every three weeks prior to receiving chemotherapy (day –1 or day 1 of each cycle). In case of fever ≥ 38.5°C, the CBC and differential must be performed and repeated every 2 days until recovery with temperature < 38.5°C or absolute neutrophil count ≥ 1.5

*Physical exam will be performed at day 1 or –1 of the cycle.

** Signs and symptoms will be recorded for baseline in the appropriate CRFs and for ALL other visits in the Clinical Adverse Experience CRF.

***Concomitant medication will be recorded for baseline on the appropriate CRFs, and will include all medication used within one month prior to registration. For ALL other visits concomitant medication will be captured ONLY if related to adverse events.

**** The End of Chemotherapy evaluation will be performed at 21 to 28 days after the last dose of chemotherapy (including patients that did not complete all cycles)

***** see Appendix 6 for follow up schedule

APPENDIX 6 - FOLLOW UP VISIT FLOW CHART

FUP timing		Required assessments		
AC→T Arm	TAC Arm	Physical exam	Mammography or Ultrasound	QOL and socio-eco
	1.5 months*	X		X
3 months	4.5 months	X		
6 months	7.5 months	X		X
9 months	10.5 months	X		
12 months	13.5 months	X	X (1)	X
15 months	16.5 months	X		
18 months	19.5 months	X		
21 months	22.5 months	X		
24 months	25.5 months	X	X (1)	X
2. 5 years	31.5 months	X		
3 years	37.5 months	X	X (1)	
3. 5 years	43.5 months	X		
4 years	49.5 months	X	X (1)	
4. 5 years	55.5 months	X		
5 years	61.5 months	X	X (1)	
6 years	73.5 months	X	X (1)	
7 years	85.5 months	X	X (1)	
8 years	97.5 months	X	X (1)	
9 years	109.5 months	X	X (1)	
10 years	121.5 months	X	X (1)	

*Named asFup1a

(1): Contra lateral mammography should be performed within +/- 6 months compared to the theoretical date.

Note: Follow up visits are calculated according to the date of the End of Chemotherapy visit.
Visits could occur within a 7-day window prior or post the projected visit date.

Note: 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.

ABBREVIATED FOLLOW UP

In case of administration of any systemic therapy (chemotherapy, hormonotherapy, genetherapy or immunotherapy) given for Breast cancer relapse or 2nd primary malignancy (excluded are non-melanoma skin cancer, in situ carcinoma of the cervix and in-situ carcinoma of the breast (LCIS/DCIS) other than the agents outlined in the protocol, patients will be followed in an abbreviated follow-up for :

- Survival
- Congestive Heart Failure.

Abbreviated follow-up visits will be done yearly at the anniversary date of EOC until year 10 after EOC or until death.

Clinical Adverse Experiences evaluated during the Abbreviated Follow up include the ones possibly or probably related to the study drug at the End of Chemotherapy or relevant non cancer related signs and symptoms occuring after the completion of chemotherapy (i.e. congestive heart failure, toxicities related to Tamoxifen and/or radiotherapy).

APPENDIX 7 - SAMPLE PATIENT INFORMED CONSENT

A MULTICENTER PHASE III RANDOMIZED TRIAL COMPARING DOCETAXEL IN COMBINATION WITH DOXORUBICIN AND CYCLOPHOSPHAMIDE (TAC) VERSUS DOXORUBICIN AND CYCLOPHOSPHAMIDE (FOLLOWED BY DOCETAXEL (AC→T) AS ADJUVANT TREATMENT OF OPERABLE BREAST CANCER HER2NEU NEGATIVE PATIENTS WITH POSITIVE AXILLARY NODES. BCIRG 005

Study number: BCIRG 005
TAX GMA 301

Investigator name:

Address:

Consent Form:

This consent form is part of the informed consent process. It is designed to give you an idea of what this research study is about and what will happen to you if you choose to be in the study. If you would like to know more about something mentioned in this form, or have any questions regarding this research study, please be sure to ask your doctor or nurse. Read this form carefully to make sure you understand all the information it provides. You will get a copy of this form to keep. This study is sponsored by Aventis and coordinated by the Breast Cancer International Research Group (BCIRG). Aventis is the company that manufactures the drug Taxotere®. Aventis will supply this drug free of charge for the purpose of this study. This study will take place at various centers throughout Canada, US, South America, Asia, Australia, South Africa and Europe. Approximately 3,130 subjects will be participating in the study. Your doctor, who is one of the researchers, will discuss the study with you. Your participation in this study is entirely voluntary. You do not have to take part in this study and your care does not depend on whether you take part or not. This study may not help you directly, but we hope that it will teach us something that will help others in the future.

BACKGROUND Information:

Your doctor has explained that you have breast cancer with a risk of relapse (cancer may return or spread after it was treated). There are several treatments which may help you. Taxotere® (docetaxel) has been administered in approximately 2,000 patients with advanced breast cancer in a clinical trial setting 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 breast cancer relapse.

Study Purpose:

The aim of the study is to see how effective docetaxel in combination with doxorubicin and cyclophosphamide (TAC) administered concomitantly is in your disease compared to doxorubicin and cyclophosphamide followed by docetaxel (AC→T) administered sequentially, which is also an effective treatment in your disease. You will have an equal chance of being treated either TAC or AC→T. The decision as to which treatment you receive will be made by chance.

Patient Initials ____
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Eligibility:

Tissue from your tumor at the time of your surgery will need to be taken and tested by a central lab, designated by the BCIRG for the presence of human epidermal growth factor receptor 2 (HER2), a protein. If it is found that you do not express this protein you will be eligible for this study.

Study Design:

If you choose to take part in this study, you have to come to the center every 3 weeks for 18 to 24 weeks.

A cycle of therapy consists of 21 days / 3 weeks. You will receive a maximum of 6 cycles if you are treated with the TAC combination and a maximum of 8 cycles (i.e.4 AC and 4T) if you are treated with the AC→T combination.

Chemotherapy Administration:

If you are treated with the TAC regimen you will receive on day 1 of the cycle the following:

- Doxorubicin 50mg/m^2 administered IV over 15 min
- Cyclophosphamide 500mg/m^2 IV administered over 5 minutes to 60 minutes
- Docetaxel 75mg/m^2 administered IV over one hour
- Every 3 weeks for 6 cycles

If you are treated with the AC→T combination you will receive the following:

- Doxorubicin 60mg/m^2 IV over 15 minutes.
- Cyclophosphamide 600mg/m^2 IV over 5 minutes to 60 minutes
- Every 3 weeks for 4 cycles

Three weeks after the 4th cycle you will receive:

- Docetaxel 100mg/m^2 IV over 1 hour for another 4 cycles every 3 weeks.

In case you develop side effects from the chemotherapy your doctor may reduce the dose of the drugs and/or delay the cycle before stopping treatment. You will be offered an alternative treatment in case chemotherapy is stopped.

Oral medication will be given twice daily for 3 days starting the night before Taxotere® to prevent hypersensitivity reaction (allergy). You will also be given drugs to prevent nausea and vomiting as well as extra fluid given by vein in order to prevent kidney damage and take an antibiotic (such as ciprofloxacin) to reduce the risk of infection when your white blood cell count is low.

Patient Initials ____

Tamoxifen is a hormonal agent that has been shown to decrease the risk of a relapse in those patients whose tumor expresses estrogen and/or progesterone receptor when it is taken for 5 years. Clinical trials have clearly demonstrated that 5 years of Tamoxifen administration is better than a shorter administration time.

Your tumor will be tested to check if it has estrogen and/or progesterone receptors. If it does, Tamoxifen will be prescribed at 20 mg daily for 5 years starting 3-4 weeks after the last course of chemotherapy for patients who have positive estrogen and/or progesterone receptors.

If while on Tamoxifen you experience severe hot flushes, vaginal bleeding, vaginal discharge or thromboembolic events, your doctor might choose to switch your treatment from Tamoxifen to anastrozole.

For postmenopausal patients without contraindications to the use of Tamoxifen, your doctor is allowed to administer a sequential therapy consisting of Tamoxifen for 2 to 3 years followed by anastrozole or exemestane for a maximum of 5 years of hormonal therapy.

The total duration of the hormonal therapy, i.e. tamoxifen followed by anastrozole, should not exceed 5 years.

For postmenopausal patients who have completed 5 years of tamoxifen, your doctor is allowed to continue the hormonal treatment with letrozole for a maximum of 3 years.

Anastrozole (Arimidex®) is a hormonal agent recently approved in the USA by the Food and Drug Administration (FDA) as adjuvant treatment for postmenopausal patients whose tumors have positive estrogen and/or progesterone receptors. In a recently published trial (ATAC trial) which compared Tamoxifen with anastrozole or combination therapy (Tamoxifen + anastrozole) among 9366 patients, Anastrozole at 1 mg/daily by oral route was shown to decrease the breast cancer recurrence rate with a follow up of more than 5 years. It has however to be noted that in a subset analysis of patients who had had previous chemotherapy, the beneficial effect of anastrozole versus tamoxifen with respect to time to recurrence was not apparent.

In addition, two large studies have recently shown a decrease of breast cancer recurrence in post-menopausal patients who switched to anastrozole or exemestane, another hormonal agent belonging to the same family as anastrozole, after 2 or 3 years of tamoxifen for a total of 5 years of hormonal treatment in comparison to 5 years tamoxifen.

Finally, a large study has also demonstrated a decrease of breast cancer recurrence in post-menopausal patients who continued the hormonal treatment with letrozole, a hormonal agent belonging to the same family as anastrozole and exemestane, for 3 years after the completion of 5 years tamoxifen.

Both exemestane and letrozole have been recently approved by the FDA for the adjuvant treatment of post-menopausal patients whose tumor is hormone receptor positive after 2-3 years or 5 years of tamoxifen, respectively. According to local authorities they were also approved for adjuvant and advanced treatment of post menopausal women with Hormone receptor positive.

Your doctor will discuss with you which of the above-mentioned hormonal treatment is more suitable for you, based on your past medical history, as well as your current medical condition, and according to the treatment approved in your country.

Radiation therapy may be given after the cycles of chemotherapy treatment has been completed, as prescribed by your doctor. It consists of radiation administration to the involved breast and the local region surrounding it. Radiation therapy has been shown to decrease the risk of local breast cancer relapse in patients who have had a lump or lymph nodes removed from the axilla. Once the original tumor is removed by surgery, the remaining breast tissue will be irradiated in order to prevent a recurrence of local disease. On the other hand, if you have had the entire breast removed, radiation might also be given to you. Your doctor in this case will explain to you if radiation therapy should be considered.

Patient Initials ____

INVESTIGATIONS DURING THE STUDY

A blood test will be done before the study begins and before each course of chemotherapy to check your blood count and blood chemistry. Each sample of blood will be 2 to 3 teaspoons. 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 to 24 weeks (i.e. 6 to 8 infusions).

A physical examination and a number of tests (scans and X-rays), including heart function tests (MUGA test or echocardiography and ECG) will be done before you start the study, during the study and the follow up period at the discretion of your doctor. A pregnancy test will be done before you receive any chemotherapy if there is a chance that you might become pregnant. If you have had only your uterus removed and are equal or under 55 years of age, a special test to check your hormonal levels and menopausal status will be done. Chemotherapy and tamoxifen therapy could affect an unborn child so it is very important that you do not get pregnant while receiving these treatments. Your doctor will talk with you about methods of birth control if you are of childbearing age. If you think that you might be pregnant, call the doctor or nurse whose phone numbers are on the last page of this form.

You will be asked to fill in quality of life questionnaires and a productivity and time loss questionnaire (in selected countries) before chemotherapy begins, at cycle 4 for the two treatment arms, at the end of the chemotherapy cycles (3 to 4 weeks after the last cycle), and at 6, 12 and 24 months of follow-up. For the AC® T additional quality of life and socio-economic questionnaires will be completed at cycle 7. If you are treated with TAC, additional questionnaires will be done at 7 weeks after the end of your chemotherapy treatment. If you were to have a Breast cancer relapse, you will be asked to complete the questionnaires at that time. The quality of life questionnaires will ask you how you feel regarding the treatment of your disease and help your doctor to judge the efficacy assessed by medical means against the benefit you feel. The productivity and time loss questionnaire will ask you what are your employment status and the time loss from work and other activities because of your illness and treatment.

Thereafter your physician will follow you in the same way as other breast cancer patients in order to confirm that the cancer has not relapsed. You will be prescribed hormonotherapy (Tamoxifen) if needed. You will receive Tamoxifen only if you will test positive for estrogen and/or progesterone receptors. This test will be done before you enter the study.

Please consult your study doctor/ nurse before taking any new prescription or non-prescription medication while on study.

Investigations during Follow Up:

The follow up will take place at the end of the study (one month after the last infusion) as well as every 3 months thereafter for the first 2 years, every 6 months years 3 to 5 and every year up to year 10.

For the first 2 years, you will have a physical examination and you will be asked to complete quality of life questionnaires and a productivity and time loss (in selected countries) at 6, 12 and 24 months of follow-up. Every 12 months a mammography will be performed.

For years 3 to 5, you will be assessed every 6 months by physical exam and every 12 months a mammography will be added.

For years 6 to 10, visits will be performed every 12 months, including physical examination and mammography. 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.

Patient Initials ____

SIDE EFFECTS

Every treatment can have side effects. Even the standard treatment has side effects, which your doctor will explain to you. It is important that you know the possible side effects of the treatments given in this study. The following are the side effects of each drug used in this study. These side effects may or may not be more severe when the drugs are taken together. These are the side effects we know about at present. However, since this is a study of new treatments there may be other side effects that we do not know about yet. It is therefore important that you report immediately to your study doctor/ nurse the occurrence of any unusual symptoms.

With Taxotere®, 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 from 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.

With doxorubicin, you may have the following side effects: blood test changes which may render 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, blood test changes that may render you more prone to infection and bruising. There is a very remote risk in developing a secondary leukemia with cyclophosphamide. However, the benefit of this treatment does outweigh the risk of developing leukemia.

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 occur.

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

If you have a fever and/or infection, 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. You may be asked to learn how to give yourself these injections.

If you are taking Tamoxifen, hot flashes and/or vaginal discharge are likely to occur. You may also experience constipation or pain with intercourse, problems controlling your bladder when you cough or sneeze. On rare occasions, serious side effects may occur. These can include uterine cancer or abnormal non-cancer cell growth in the pelvic area that may cause pain or bleeding; eye problems (including cataracts, a clouding of the lens inside the eye); liver cancer or changes in blood tests that show possible liver damage; stroke; and blood clots in areas such as the legs, the eyes, or the lungs that could be life-threatening.

Patient Initials ____

With **Anastrozole**, you may experience: hot flushes, joint and/or muscle pain, fatigue, mood disturbances, nausea/vomiting, fractures; vaginal bleeding and vaginal discharge less frequent than under tamoxifen.

With Letrozole, you may experience: hot flashes, headache, loss of appetite, general pain, weakness, nausea, or diarrhea.

With Exemestane, you may experience: sweating, fatigue, swelling,hot flashes, mood alteration, abdominal pain, nausea, or diarrhea.

If you receive radiation therapy, the most common side effects will be skin burns, skin tenderness, fibrosis in the area being irradiated. Fatigue is also common.

INTRAVENOUS NEEDLES AND BLOOD WORK:

Some known risks, although rare, are associated with placing a needle into a vein or under the skin. These include discomfort, the possibility of infection, and may leave a temporary bruise, or swelling.

MANDATORY TESTING ON YOUR TISSUE SAMPLE

Tumor material taken at time of your recent surgery (ies) will be sent to a laboratory that Breast Cancer International Research Group (BCIRG) will designate in order to confirm that your cancer has not the amplification of the HER2 gene. We also will repeat some standard tests already performed on your tumor at the site where you are being treated. These standard tests include histologic subtype, differentiation grade, vascular invasion, tumor size, estrogen and progesterone receptors.

ADDITIONAL TESTING ON YOUR TISSUE SAMPLE

We are now asking you for permission to store your tumor sample and use it to measure certain markers in the future. Markers are substances made by breast cancer cells. It has been found that there is a correlation between some markers in certain types of cancers and the treatment response. There will be a number of these measurements which will be made on your tumor material in order to determine a possible correlation with the benefit that you will have from the treatment you receive during this study. The markers that will possibly be tested are: p53, members of the Bcl family (Bcl-2, Bax, Bcl-x and Bag-1), MUC1, MIB1 and tubulin isoforms (particularly II, III, IV and Tau). 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.

Patient Initials ____

Should you (or your legally authorized representative) not wish the scientists to use your tumor sample, refusing to grant permission for testing of these other markers will not affect either your participation in BCIRG 005 trial or the quality of the care you will receive as a participant in this study in any way. Your tumor sample will be returned to your doctor once the mandatory testing for HER2neu has been performed, and the repetition of the standard tests.

The results of the marker testing may not help you directly now, or in the future. The research will not have an effect on your care. 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 samples will be kept for 10 years. 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. The results of the markers will not be given to you or your doctor during the course of your participation in this study unless specifically requested. This information will not be put in your health record.

You can request at any time that your tissue not be used any longer for research. You need to contact your study doctor and let him know that you do not want us to use your tissue. The tissue will no longer be used for research.

Do you agree to have your tumor sample stored and used to measure the markers currently identified in the study and for markers identified in the future? Please circle your answer.

YES NO

Patient Initials: _____

STANDARD TREATMENTS

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 do not wish to participate in this study, there are other treatments available to you. Your doctor will discuss with you other treatment options available to patients with your type of cancer and explain the risks and benefits of these options to you. Right now, the usual treatment is to use any or all of the standard therapies, other drugs and procedures or other investigational drugs. The doctors can provide detailed information about this and the benefits of various treatments available to you. Other therapies which are optional to you may not be curative but may control your symptoms. You may also choose to have no treatment in which case your tumor will be expected to grow.

POTENTIAL BENEFITS

Participation in this study may be of no personal benefit to you. However, based on the results of this study, it is hoped that, in the long-term, patient care can be improved.

Patient Initials ____

WITHDRAWAL FROM STUDY

In discussion with you, your doctor at the center, either at his/her own initiative or at the request from the sponsor of this study, may withdraw you from the study at any time if it is in your best interests. You may also withdraw from the study at any time if you wish to do so.

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

COSTS

You will not have to pay for the treatment you receive in this study. If you are covered by a private insurance company, you will get some or all of your money back, but if you do not have private insurance, the sponsors of this study will cover these costs. In the same way, you will have to pay for the drugs you need for side effects, such as your anti-nausea medications. You will be coming to the cancer center more often than if you were not part of a study. There may be some extra costs, such as parking and meals that you will have to pay.

INJURY CLAUSE

It is important to note that nothing said in this consent form alters your legal rights to recover damages. However, if you suffer an injury as a result of participating in this research because of the negligence of the sponsor, the policy of the study sponsor is to pay for all medical treatments (or services) recommended by your doctors that are not covered by health insurance (e.g. Medicare). While Aventis makes no commitment to provide compensation beyond this point, you retain all your legal rights to pursue other possible avenues of compensation (e.g. legal action).

If you have any questions regarding a research-related injury or other medical concerns, or any further inquiries concerning the procedures of this study, you should contact:

Doctor name: _____ Telephone number: _____
Study Coordinator name: _____ Telephone number: _____

For information concerning research and your rights as a study participant, you should contact:

Name and phone number of patient representative or ethics committee contact person:

_____

Patient Initials ____
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CONFIDENTIALITY

The information that we collect as part of this study will be shared with other researchers and doctors. However, you will not be identified in any of these reports. Data and materials collected as part of this study, and some information from your original medical records as it relates to this study, may need to be sent to the statistical headquarters of BCIRG. Strict confidentiality will be maintained and you will not be identified by name on any of the data and materials submitted. Your identity will not be revealed except if required by law. We will keep all the material we collect for this study in a safe storage area.

Representatives from the Ethics Committee, the government, the Canadian Health Protection Branch or the Food and Drug Administration in the United States or other Regulatory authorities around the world, BCIRG and the sponsor Aventis may want to look at your medical record as it relates to this study at the center. This is part of the process of quality control. Each person looking at your records will follow the relevant center's policies and procedures that control these actions.

PATIENT CONSENT

I have been informed of the purpose, procedures and duration of the study (BCIRG 005) 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 (Print)

_____

Signature of Patient

_____

Date

_____

Name of Investigator (Print)

_____

Signature of Investigator:

_____

Date

_____

APPENDIX 8 - SERIOUS ADVERSE EVENT REPORT FORM

Aventis

SAE/ER* from a Clinical Trial

Study No.				Investigator's No.		Patient No.	Country
Patient Initials			Date of Birth			Age	Sex	Height (cm)	Weight (kg)
first	mid	last	day	month	year		☐ male ☐ female		

Criteria for expedited reporting (tick all applicable)

Seriousness criteria:

- ☐ was life threatening
- ☐ required or prolonged inpatient hospitalization
- ☐ was persistently or significantly disabling/incapacitating
- ☐ is a congenital anomaly
- ☐ resulted in death
- ☐ is medically important

Alert Term ☐ No ☐ Yes

If the event is serious, make sure to tick the appropriate seriousness criterion

Did the patient take a significant overdose? ☐ No ☐ Yes

Date and type of report

Date of THIS report |__|__| |__|__| |__|__|__|__|
(day) / (month)/ (year)

Date reported to Investigator |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Report type: ☐ initial ☐ follow up

For follow-up report, give only changes to previous

Adverse event number |__|__|__|__|
(AE# in study book for the same AE)

Was this serious adverse event first reported as a non-serious adverse event? ☐ No ☐ Yes

IF YES, Date event became serious |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

If event started BEFORE first dose of study medication

Did this event continue and worsen in intensity (severity and/or frequency) after the first dose of study medication? ☐ No ☐ Yes

Description of adverse event and duration

Diagnosis/syndrome of AE

_____

Component signs or symptoms (only if applicable) 1. _____ 2. _____
3. _____ 4. _____ 5. _____

Start of adverse event |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

End of adverse event |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Duration if adverse event lasted less than 24 hours: |__|__|__| |__|__| |__|__|
(hours) / (minutes) / (sec)

Time since last dose of study medication |__|__|__| |__|__|
(hours) / (minutes)

Comments on adverse event:

_____

*SAE = serious adverse event, ER = expedited report

Aventis

SAE/ER from a Clinical Trial

Comments continued _____

_____

_____

_____

_____

_____

Remedial measures

Study medication (select one)

- ☐ no change
- ☐ dosage increased due to event
- ☐ dosage decreased due to event
- ☐ discontinued and reintroduced, no event recurred
- ☐ discontinued and reintroduced, same event recurred
- ☐ discontinued and reintroduced, different event occurred
- ☐ discontinued due to event and subject withdrawn
- ☐ permanently discontinued for other reason
- ☐ other, *please specify* _____

_____

Were there other countermeasures? ☐ No ☐ Yes

If YES, Medication ☐ No ☐ Yes

Other *(please specify)* _____

_____

Causal relationship

Is there a reasonable possibility that the adverse event is associated with the study medication?

☐ No ☐ Yes

Whether NO or YES, an alternative explanation may be ticked and details given below:

- ☐ underlying/concomitant illness
- ☐ possibly associated with concomitant drug(s)
- ☐ directly related to study procedures
- ☐ other known or suspected cause *(please comment)*

_____

_____

Intensity

- ☐ mild
- ☐ moderate
- ☐ severe

Outcome

- ☐ recovery without sequelae
- ☐ recovery with sequelae
- ☐ ongoing at time of report
- ☐ event not resolved, follow-up not deemed necessary by investigator
- ☐ subject died

Relevant medical history (e.g. previous diseases, surgery, allergies, pregnancy)

_____

Study medication: _____

(1) ☐ study medication (2) ☐ active comparator
(3) ☐ placebo (4) ☐ code not broken

Date started |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Indication _____

Date ended |__|__| |__|__| |__|__|__|__|
(day) / (month) / (year)

Daily dose _____ Unit _____ Route _____ Batch No. _____

*SAE = serious adverse event, ER = expedited report

GREGU-GPE-SD-07-01

Approval Date: October 25, 2000

"SAE/ER from a Clinical Trial" Form (version 2)

Aventis

SAE/ER from a Clinical Trial

Concomitant medication
(List all drugs even if listed elsewhere in study book; exclude those given to treat adverse event)

Drug	Daily dose	Unit	Route	Indication	Date started day / month / year	Date stopped day / month / year	Ongoing No Yes	*Causal relationship No Yes
[1]								
[2]								
[3]								
[4]								
[5]								
[6]								
[7]								
(8]								
[9]								

**Is there a reasonable possibility that the adverse event is associated with the concomitant medication?*

In case of death

Date of death |__|__| |__|__| |__|__|__|__| (day) / (month) / (year)	Was an autopsy performed? ☐ No ☐ Yes ☐ planned *If YES, please provide a copy of the autopsy report*
Was the death related to the study medication?	☐ No ☐ Direct consequence ☐ Indirect consequence
Cause of death *(tick all applicable)* No Yes Disease for which subject was enrolled into study ☐ ☐ Other pre-existing condition(s) ☐ ☐ Serious adverse event ☐ ☐ Unknown ☐ ☐ *(Further information will be requested)*	Cause(s) of death ranked in order of likelihood 1. _____ 2. _____ 3. _____ 4. _____
Investigator Name and address:	Investigator Date (day/month/year): Signature:
MON Date received (day/month/year): Name: Signature:	Affiliate Safety Officer Date received (day/month/year): Name: Signature:
International drug surveillance number (to be filled out by company)	Clintrace Entry Site Date report received:

*SAE = serious adverse event, ER = expedited report

GREGU-GPE-SD-07-01 Approval Date: October 25, 2000
"SAE/ER from a Clinical Trial" Form (version 2)

APPENDIX 9 – TAXOTERE® DRUG SUPPLY

Implementation Of The Taxotere® With New Storage Conditions

Implementation of the Taxotere® with new storage conditions for clinical trials is following the implementation on the Market. First Market supplied is the European Community*, plus Norway and Switzerland.

In these first countries, for Clinical trials, Taxotere® stored between +2°C to +8°C will be replaced by Taxotere® stored between +2°C to + 25 °C. Locally, Taxotere® stored between +2°C to +8°C will be used until inventories are depleted.

Supplies for Clinical trials of the Taxotere® with new storage conditions will be implemented progressively, depending on Local Approval, and Market Launch.

For a short period, inventories of Taxotere® stored between +2°C to +8°C and inventories of Taxotere® stored between +2°C to + 25 °C will be available at the same investigational sites. We suggest not to mix premix solution of Taxotere® stored between +2°C to +8°C, and premix solution of Taxotere® stored between +2°C to +25°C. In case it happens, the period for use of the premix and the infusion bags will be the shortest, corresponding to the instructions for use of Taxotere® stored between +2°C to +8°C.

- * European Community

Austria
Belgium
Denmark
Finland
France
Germany
Greece
Ireland
Italia
Luxemburg
Portugal
Spain
Sweden
The Netherlands
United Kingdom

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

Storage Conditions + 2° C and +8 °C

~~3.~~ 1. Drug substance

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

2. Formulations

TAXOTERE® concentrate for solution 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(II):
PREPARATION GUIDE FOR USE WITH TAXOTERE® CONCENTRATE AND SOLVENT FOR SOLUTION FOR INFUSION FOR TAXOTERE®

Storage Conditions + 2° C and +25 °C

1. Drug Substance

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

2. Formulations

TAXOTERE® concentrate for solution 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:

Vials should be stored between +2°C and +25°C and 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. However the chemical and physical stability of the premix solution has been demonstrated for 8 hours when stored either between +2°C and +8°C 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 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 used within 4 hours and should be aseptically administered as a 1-hour infusion under room temperature and normal lighting conditions.

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.

POLYSORBATE 80 (TWEEN 80®) CONTAINING DRUGS

VEPESID®	ETOPOSIDE
DEPO-PROVERA®	MEDROXYPROGESTERONE ACETATE
DEPO-PRODASONE® 500 - 250mg	MEDROXYPROGESTERONE
DEXTANCYL®	DEXAMETHASONE
DIPROSTENE®	BETAMETHASONE
HYDROCORTANCYL®	PREDNISOLONE (ACETATE)
HYDROCORTANCYL (Roussel)®	HYDROCORTISONE (ACETATE)
CORTISONE (Roussel)® 25, 125 mg	CORTISONE (ACETATE)
ALTIM®	CORTIVASOL
TEDAROL® 50 mg	TRIAMCINOLONE
KENACORT - retard®	TRIAMCINOLONE
ARISTOPAN®	TRIAMCINOLONE
DURACILLIN A.S.®	PENICILLINE
LIBRIUM®	CHLORODIAZEPOXIDE
E. FEROL®	VITAMINE E
CORBIONAX®	AMIODARONE
ACTILYSE® 20, 50 mg	T.P.A. (Activateur tissulaire du plasminogene)
DECAPEPTYL®	TRIPTORELINE
ORTHOCLONE OKT3®	
TERPONE®	ESSENCES TERPENIQUES
VACCIN GENHEVAC B® (Pasteur)	

APPENDIX 10 – QUALITY OF LIFE

EORTC QLQ-C30 and QLQ-BR23

The English versions of the QLQ-C30 (version 3.0), QLQ-BR 23 (version 1.0) and the Euroquol (EQ-5D) follow.

Note: The questionnaires are available in the following languages.
Bulgarian
Chinese (Taiwanese)
Croatian
Czech
Danish
Dutch
English
Finnish
French
German
Hebrew
Hungarian
Indian (Hindi)
Indian (Gujarathi)
Indian (Marathi)
Iranian
Italian
Japanese
Lithuanian
Norwegian
Polish
Portugese
Russian
Serbian
Slovenian
Spanish
Swedish
Turkish

EORTC QLQ-C30 (version 3.0)

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):

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

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 A Quite Very

		All	Little	a Bit	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

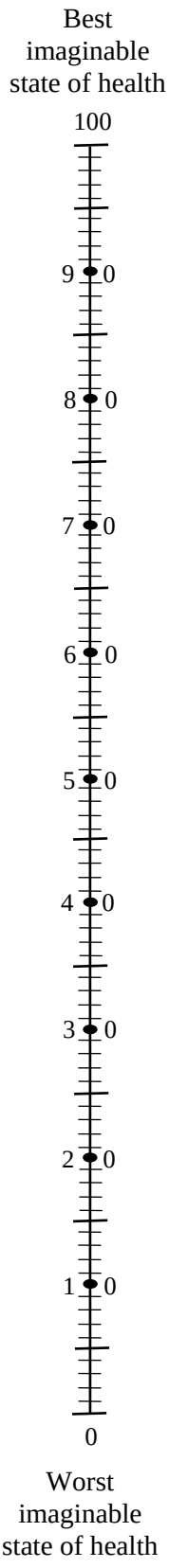
During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Did you have any pain in your arm or shoulder?	1	2	3	4
48.	Did you have a swollen arm or hand?	1	2	3	4
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	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

Euroquol (EQ-5D)

To help people say how good or bad their state of health is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

Your own state of health today



By placing a check-mark in one box in each group below, please indicate which statements best describe your own state of health today.

Mobility

I have no problems in walking about	❑
I have some problems in walking about	❑
I am confined to bed	❑

Self-Care

I have no problems with self-care	❑
I have some problems washing or dressing myself	❑
I am unable to wash or dress myself	❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities	❑
I have some problems with performing my usual activities	❑
I am unable to perform my usual activities	❑

Pain/Discomfort

I have no pain or discomfort	❑
I have moderate pain or discomfort	❑
I have extreme pain or discomfort	❑

Anxiety/Depression

I am not anxious or depressed	❑
I am moderately anxious or depressed	❑
I am extremely anxious or depressed	❑

APPENDIX 11 – PRODUCTIVITY AND TIME LOSS QUESTIONNAIRE

Will be done in selected countries

PRODUCTIVITY AND TIME LOSS QUESTIONNAIRE

To be completed by the patient. This questionnaire is important and should only take 1-2 minutes to complete.

Patient Initials: | | | Date of Birth: dd / mm / yyyy Today's date: dd / mm / yyyy

EMPLOYMENT STATUS

Which category best describes your current state?

- ☐ Employed
  - ☐ 1 with leave of absence
  - ☐ 2 without leave of absence
- ☐ 3 Unemployed
- ☐ 4 Retired
- ☐ 6 Homemaker
- ☐ 7 Student
- ☐ 5 Other (specify) _____

If employed, on average how many hours per week do you work? _____ (hours per week)

TIME LOST FROM WORK AND OTHER ACTIVITIES

Because of your illness and treatment, you may or may not experience time losses in your work and other activities, including leisure and housework.

If you are employed and do not have a leave of absence from work, how many days have you missed from work within the last week?

_____ (days)

On average, which category best describes restrictions (if any) from performing usual activities within the last week.

- ☐ 1 No (0%) Restriction
- ☐ 2 Some (25%) Restriction
- ☐ 3 Moderate (50%) Restriction
- ☐ 4 Severe (75%) Restriction
- ☐ 5 Total (100%) Restriction

APPENDIX 12 - HEMATOLOGY NORMAL LABORATORY VALUES

Test	Lower limit	Upper limit	Units
Hemoglobin	12.00 (F)	15.60 (F)	g/dL
Platelets	150.00	400.00	10^9/L
White Blood Cells	4.00	10.00	10^9/L
Neutrophils	2.00	6.00	10^9/L
Lymphocytes	2.00	4.00	10^9/L
Monocytes	0.20	0.95	10^9/L
Eosinophils	0.04	0.60	10^9/L
Basophils	0.01	0.05	10^9/L
Atypical lymphocytes	< 0		

The table above is to inform you of the standard normal ranges which will be used to analyse hematological parameters for the study. The standard values have been taken from NCI Common Toxicity Criteria (Version 2.0) and Clinical Decisions for Lab Tests by B.E. Statland, published by Medical Economics Books, 1987 when not defined in the NCI Common Toxicity Criteria, version 2.0.

APPENDIX 13 - NCI COMMON TOXICITY CRITERIA, version 2.0

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
ALLERGY/IMMUNOLOGY					
Allergic reaction/ hypersensitivity (including drug fever)	none	transient rash, drug fever < 38°C (<100.4°F)	urticaria, drug fever ≥ 38°C (≥100.4°F), and/or asymptomatic bronchospasm	symptomatic bronchospasm, requiring parenteral medication(s), with or without urticaria; allergy-related edema/angioedema	anaphylaxis
Note: Isolated urticaria, in the absence of other manifestations of an allergic or hypersensitivity reaction, is graded in the DERMATOLOGY/SKIN category.					
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	none	mild, not requiring treatment	moderate, requiring treatment	-	-
Autoimmune reaction	none	serologic or other evidence of autoimmune reaction but patient is asymptomatic (e.g., vitiligo), all organ function is normal and no treatment is required	evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism), requiring treatment other than immunosuppressive drugs	reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia), requiring short-term immunosuppressive treatment	autoimmune reaction causing major grade 4 organ dysfunction; progressive and irreversible reaction; long-term administration of high-dose immuno-suppressive therapy required
Also consider Hypothyroidism, Colitis, Hemoglobin, Hemolysis.					
Serum sickness	none	-	-	present	-
Urticaria is graded in the DERMATOLOGY/SKIN category if it occurs as an isolated symptom. If it occurs with other manifestations of allergic or hypersensitivity reaction, grade as Allergic reaction/hypersensitivity above.					
Vasculitis	none	mild, not requiring treatment	symptomatic, requiring medication	requiring steroids	ischemic changes or requiring amputation
Allergy/Immunology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
AUDITORY/HEARING					
Conductive hearing loss is graded as Middle ear/hearing in the AUDITORY/HEARING category.					
Earache is graded in the PAIN category.					
External auditory canal	normal	external otitis with erythema or dry desquamation	external otitis with moist desquamation	external otitis with discharge, mastoiditis	necrosis of the canal soft tissue or bone
Note: Changes associated with radiation to external ear (pinnae) are graded under Radiation dermatitis in the DERMATOLOGY/SKIN category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Inner ear/hearing	normal	hearing loss on audiometry only	tinnitus or hearing loss, not requiring hearing aid or treatment	tinnitus or hearing loss, correctable with hearing aid or treatment	severe unilateral or bilateral hearing loss (deafness), not correctable
Middle ear/hearing	normal	serous otitis without subjective decrease in hearing	serous otitis or infection requiring medical intervention; subjective decrease in hearing; rupture of tympanic membrane with discharge	otitis with discharge, mastoiditis or conductive hearing loss	necrosis of the canal soft tissue or bone
Auditory/Hearing-Other (Specify, _____)	normal	mild	moderate	severe	life-threatening or disabling
BLOOD/BONE MARROW					
Bone marrow cellularity	normal for age	mildly hypocellular or 25% reduction from normal cellularity for age	moderately hypocellular or >25 - ≤ 50% reduction from normal cellularity for age or >2 but <4 weeks to recovery of normal bone marrow cellularity	severely hypocellular or >50 - ≤ 75% reduction in cellularity for age or 4 - 6 weeks to recovery of normal bone marrow cellularity	aplasia or >6 weeks to recovery of normal bone marrow cellularity
Normal ranges:					
children (≤ 18 years)	90% cellularity average				
younger adults (19-59)	60-70% cellularity average				
older adults (≥ 60 years)	50% cellularity average				
Note: Grade Bone marrow cellularity only for changes related to treatment not disease.					
CD4 count	WNL	< LLN - 500/mm^3	200 - < 500/mm^3	50 - < 200/mm^3	< 50/mm^3
Haptoglobin	normal	decreased	-	absent	-
Hemoglobin (Hgb)	WNL	< LLN - 10.0 g/dl < LLN - 100 g/L < LLN - 6.2 mmol/L	8.0 - < 10.0 g/dL 80 - < 100 g/L 4.9 - < 6.2 mmol/L	6.5 - < 8.0 g/dL 65 - 80 g/L 4.0 - < 4.9 mmol/L	< 6.5 g/dL < 65 g/L < 4.0 mmol/L
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic processes	WNL	10 - <25% decrease from pretreatment	25 - <50% decrease from pretreatment	50 - <75% decrease from pretreatment	≥75% decrease from pretreatment
Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis, other)	none	only laboratory evidence of hemolysis [e.g., direct antiglobulin test (DAT, Coombs') schistocytes]	evidence of red cell destruction and ≥ 2gm decrease in hemoglobin, no transfusion	requiring transfusion and/or medical intervention (e.g., steroids)	catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)
Also consider Haptoglobin, Hemoglobin.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Leukocytes (total WBC)	WNL	< LLN - 3.0 x 10^9 /L < LLN - 3000/mm^3	≥2.0 - < 3.0 x 10^9 /L ≥2000 - < 3000/mm^3	≥1.0 - < 2.0 x 10^9 /L ≥1000 - < 2000/mm^3	< 1.0 x 10^9 /L < 1000/mm^3
For BMT studies:	WNL	≥2.0 - <3.0 X 10^9/L ≥2000 - <3000/mm^3	≥1.0 - <2.0 x 10^9 /L ≥1000 - <2000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3
Note: The following criteria using age, race and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75 - <100% LLN	*≥50 - <75% LLN*	*≥25 - 50% LLN*	*<25% LLN*
Lymphopenia	WNL	<LLN - 1.0 x 10^9 /L <LLN - 1000/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	<0.5 x 10^9 /L <500/mm^3	-
Note: The following criteria using age, race, and sex normal values may be used for pediatric studies if the protocol so specifies.					
		≥75-<100%LLN	*≥50-<75%LLN*	*≥25-<50%LLN*	*<25%LLN*
Neutrophils/granulocytes (ANC/AGC)	WNL	≥1.5 - <2.0 x 10^9 /L ≥1500 - <2000/mm^3	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	< 0.5 x 10^9 /L < 500/mm^3
For BMT:	WNL	≥1.0 - <1.5 x 10^9 /L ≥1000 - <1500/mm^3	≥0.5 - <1.0 x 10^9 /L ≥500 - <1000/mm^3	≥0.1 - <0.5 x 10^9 /L ≥100 - <500/mm^3	<0.1 x 10^9 /L <100/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Platelets	WNL	< LLN - <75.0 x 10^9 /L < LLN - 75000/mm^3	≥50.0 - < 75.0 x 10^9 /L ≥50000 - < 75000/mm^3	≥10.0 - < 50.0 x 10^9 /L ≥10000 - < 50000/mm^3	< 10.0 x 10^9 /L < 10000/mm^3
For BMT:	WNL	≥50.0 - <75.0 x 10^9 /L ≥50000 - <75000/mm^3	≥20.0 - <50.0 x 10^9 /L ≥20000 - <50000/mm^3	≥10.0 - <20.0 x 10^9 /L ≥10000 - <20000/mm^3	<10.0 x 10^9 /L <10000/mm^3
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies or bone marrow infiltrative/ myelophthisic process	WNL	10 - <25% decrease from baseline	25 - <50% decrease from baseline	50 - <75% decrease from baseline	≥75% decrease from baseline
Transfusion: Platelets	none	-	-	yes	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
For BMT:	none	1 platelet transfusion in 24 hours	2 platelet transfusions in 24 hours	≥3 platelet transfusions in 24 hours	platelet transfusions and other measures required to improve platelet increment; platelet transfusion refractoriness associated with life-threatening bleeding. (e.g., HLA or cross matched platelet transfusions)
Also consider Platelets.					
Transfusion: pRBCs	none	-	-	Yes	-
For BMT:	none	≤2 u pRBC (≤*15mL/kg*) in 24 hours elective or planned	3 u pRBC (>*15* ≤*30mL/kg*) in 24 hours elective or planned	≥4 u pRBC (>*30mL/kg*) in 24 hours	hemorrhage or hemolysis associated with life-threatening anemia; medical intervention required to improve hemoglobin
Also consider Hemoglobin.					
Blood/Bone Marrow-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CARDIOVASCULAR (ARRHYTHMIA)					
Conduction abnormality/ Atrioventricular heart block	none	asymptomatic, not requiring treatment (e.g., Mobitz type I second-degree AV block, Wenckebach)	symptomatic, but not requiring treatment	symptomatic and requiring treatment (e.g., Mobitz type II second-degree AV block, third-degree AV block)	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Nodal/junctional arrhythmia/dysrhythmia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Palpitations	none	present	-	-	-
Note: Grade palpitations only in the absence of a documented arrhythmia.					
Prolonged QTc interval (QTc > 0.48 seconds)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus bradycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Sinus tachycardia	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment of underlying cause	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Supraventricular arrhythmias (SVT/atrial fibrillation/ flutter)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Syncope (fainting) is graded in the NEUROLOGY category.					
Vasovagal episode	none	-	present without loss of consciousness	present with loss of consciousness	-
Ventricular arrhythmia (PVCs/bigeminy/trigeminy/ ventricular tachycardia)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic and requiring treatment	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
Cardiovascular/ Arrhythmia-Other (Specify, _____)	none	asymptomatic, not requiring treatment	symptomatic, but not requiring treatment	symptomatic, and requiring treatment of underlying cause	life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)
CARDIOVASCULAR (GENERAL)					
Acute vascular leak syndrome	absent	-	symptomatic, but not requiring fluid support	respiratory compromise or requiring fluids	life-threatening; requiring pressor support and/or ventilatory support
Cardiac-ischemia/infarction	none	non-specific T-wave flattening or changes	asymptomatic, ST- and T- wave changes suggesting ischemia	angina without evidence of infarction	acute myocardial infarction
Cardiac left ventricular function	normal	asymptomatic decline of resting ejection fraction of ≥ 10% but < 20% of baseline value; shortening fraction ≥ 24% but < 30%	asymptomatic but resting ejection fraction below LLN for laboratory or decline of resting ejection fraction ≥ 20% of baseline value; < 24% shortening fraction	CHF responsive to treatment	severe or refractory CHF or requiring intubation
CNS cerebrovascular ischemia is graded in the NEUROLOGY category.					
Cardiac troponin I (cTnI)	normal	-	-	levels consistent with unstable angina as defined by the manufacturer	levels consistent with myocardial infarction as defined by the manufacturer
Cardiac troponin T (cTnT)	normal	≥ 0.03 - < 0.05 ng/mL	≥ 0.05 - < 0.1 ng/mL	≥ 0.1 - < 0.2 ng/mL	≥ 0.2 ng/mL
Edema	none	asymptomatic, not requiring therapy	symptomatic, requiring therapy	symptomatic edema limiting function and unresponsive to therapy or requiring drug discontinuation	anasarca (severe generalized edema)

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hypertension	none	asymptomatic, transient increase by >20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	recurrent or persistent or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100* if previously WNL; not requiring treatment	requiring therapy or more intensive therapy than previously	hypertensive crisis
**Note: For pediatric patients, use age and sex appropriate normal values > 95th percentile ULN.*					
Hypotension	none	changes, but not requiring therapy (including transient orthostatic hypotension)	requiring brief fluid replacement or other therapy but not hospitalization; no physiologic consequences	requiring therapy and sustained medical attention, but resolves without persisting physiologic consequences	shock (associated with acidemia and impairing vital organ function due to tissue hypoperfusion)
Also consider Syncope (fainting).					
Note: Angina or MI is graded as Cardiac- ischemia/infarction in the CARDIOVASCULAR (GENERAL) category.					
For pediatric patients, systolic BP 65 mmHg or less in infants up to 1 year old and 70 mmHg or less in children older than 1 year of age, use two successive or three measurements in 24 hours.					
Myocarditis	none	-	-	CHF responsive to treatment	severe or refractory CHF
Operative injury of vein/artery	none	primary suture repair for injury, but not requiring transfusion	primary suture repair for injury, requiring transfusion	vascular occlusion requiring surgery or bypass for injury	myocardial infarction; resection of organ (e.g., bowel, limb)
Pericardial effusion/ pericarditis	none	asymptomatic effusion, not requiring treatment	pericarditis (rub, ECG changes, and/or chest pain)	With physiologic consequences	tamponade (drainage or pericardial window required)
Peripheral arterial ischemia	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., amputation)
Phlebitis (superficial)	none	-	present	-	-
Note: Injection site reaction is graded in the DERMATOLOGY/SKIN category.					
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Syncope (fainting) is graded in the NEUROLOGY category.					
Thrombosis/embolism	none	-	deep vein thrombosis, not requiring anticoagulant	deep vein thrombosis, requiring anticoagulant therapy	embolic event including pulmonary embolism
Vein/artery operative injury is graded as Operative injury of vein/artery in the CARDIOVASCULAR (GENERAL) category.					
Visceral arterial ischemia (non-myocardial)	none	-	brief episode of ischemia managed non-surgically and without permanent deficit	requiring surgical intervention	life-threatening or with permanent functional deficit (e.g., resection of ileum)
Cardiovascular/ General-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
COAGULATION					
Note: See the HEMORRHAGE category for grading the severity of bleeding events.					
DIC (disseminated intravascular coagulation)	absent	-	-	laboratory findings present with no bleeding	laboratory findings and bleeding
Also grade Platelets.					
Note: Must have increased fibrin split products or D-dimer in order to grade as DIC.					
Fibrinogen	WNL	≥0.75 - <1.0 x LLN	≥0.5 - <0.75 x LLN	≥0.25 - <0.5 x LLN	<0.25 x LLN
Note: The following criteria may be used for leukemia studies or bone marrow infiltrative/myelophthisic process if the protocol so specifies.					
For leukemia studies:	WNL	<20% decrease from pretreatment value or LLN	≥20 - <40% decrease from pretreatment value or LLN	≥40 - <70% decrease from pretreatment value or LLN	<50 mg%
Partial thromboplastin time (PTT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Phelbitis is graded in the CARDIOVASCULAR (GENERAL) category.					
Prothrombin time (PT)	WNL	> ULN - ≤ 1.5 x ULN	> 1.5 - ≤ 2 x ULN	>2 x ULN	-
Thrombosis/embolism is graded in the CARDIOVASCULAR (GENERAL) category.					
Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura/TTP or hemolytic uremic syndrome/HUS)	absent	-	-	laboratory findings present without clinical consequences	laboratory findings and clinical consequences, (e.g., CNS hemorrhage/ bleeding or thrombosis/ embolism or renal failure) requiring therapeutic intervention
For BMT:	-	evidence of RBC destruction (schistocytosis) without clinical consequences	evidence of RBC destruction with elevated creatinine (≤3 x ULN)	evidence of RBC destruction with creatinine (>3 x ULN) not requiring dialysis	evidence of RBC destruction with renal failure requiring dialysis and/or encephalopathy
Also consider Hemoglobin (Hgb), Platelets, Creatinine.					
Note: Must have microangiopathic changes on blood smear (e.g., schistocytes, helmet cells, red cell fragments).					
Coagulation-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
CONSTITUTIONAL SYMPTOMS					
Fatigue (lethargy, malaise, asthenia)	none	increased fatigue over baseline, but not altering normal activities	moderate (e.g., decrease in performance status by 1 ECOG level or 20% Karnofsky or *Lansky*) or causing difficulty performing some activities	severe (e.g., decrease in performance status by ≥2 ECOG levels or 40% Karnofsky or *Lansky*) or loss of ability to perform some activities	bedridden or disabling
Note: See Appendix III for performance status scales.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Fever (in the absence of neutropenia, where neutropenia is defined as AGC < 1.0 x 10^9/L)	none	38.0 - 39.0°C (100.4 - 102.2°F)	39.1 - 40.0°C (102.3 - 104.0°F)	> 40.0°C (>104.0°F) for < 24hrs	> 40.0°C (>104.0°F) for > 24hrs
Also consider Allergic reaction/hypersensitivity.					
Note: The temperature measurements listed above are oral or tympanic.					
Hot flashes/flushes are graded in the ENDOCRINE category.					
Rigors, chills	none	mild, requiring symptomatic treatment (e.g., blanket) or non-narcotic medication	severe and/or prolonged, requiring narcotic medication	not responsive to narcotic medication	-
Sweating (diaphoresis)	normal	mild and occasional	frequent or drenching	-	-
Weight gain	< 5%	5 - <10%	10 - <20%	≥ 20%	-
Also consider Ascites, Edema, Pleural effusion.					
Weight gain - veno-occlusive disease (VOD)					
Note: The following criteria is to be used ONLY for weight gain associated with Veno-Occlusive Disease.					
	<2%	≥2 - <5%	≥5 - <10%	≥10% or as ascities	≥10% or fluid retention resulting in pulmonary failure
Weight loss	< 5%	5 - <10%	10 - <20%	≥20%	-
Also consider Vomiting, Dehydration, Diarrhea.					
Constitutional Symptoms-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
DERMATOLOGY/SKIN					
Alopecia	normal	mild hair loss	pronounced hair loss	-	-
Bruising (in absence of grade 3 or 4 thrombocytopenia)	none	localized or in dependent area	generalized	-	-
Note: Bruising resulting from grade 3 or 4 thrombocytopenia is graded as Petechiae/purpura and Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia in the HEMORRHAGE category, not in the DERMATOLOGY/SKIN category.					
Dermatitis, focal (associated with high-dose chemotherapy and bone marrow transplant)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include spontaneous bleeding not induced by minor trauma or abrasion

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Dry skin	normal	controlled with emollients	not controlled with emollients	-	-
Erythema multiforme (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)	absent	-	scattered, but not generalized eruption	severe or requiring IV fluids (e.g., generalized rash or painful stomatitis)	life-threatening (e.g., exfoliative or ulcerating dermatitis or requiring enteral or parenteral nutritional support)
Flushing	absent	present	-	-	-
Hand-foot skin reaction	none	skin changes or dermatitis without pain (e.g., erythema, peeling)	skin changes with pain, not interfering with function	skin changes with pain, interfering with function	-
Injection site reaction	none	pain or itching or erythema	pain or swelling, with inflammation or phlebitis	ulceration or necrosis that is severe or prolonged, or requiring surgery	-
Nail changes	normal	discoloration or ridging (koilonychia) or pitting	partial or complete loss of nail(s) or pain in nailbeds	-	-
Petechiae is graded in the HEMORRHAGE category.					
Photosensitivity	none	painless erythema	painful erythema	erythema with desquamation	-
Pigmentation changes (e.g., vitiligo)	none	localized pigmentation changes	generalized pigmentation changes	-	-
Pruritus	none	mild or localized, relieved spontaneously or by local measures	intense or widespread, relieved spontaneously or by systemic measures	intense or widespread and poorly controlled despite treatment	-
Purpura is graded in the HEMORRHAGE category.					
Radiation dermatitis	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion
Note: Pain associated with radiation dermatitis is graded separately in the PAIN category as Pain due to radiation.					
Radiation recall reaction (reaction following chemotherapy in the absence of additional radiation therapy that occurs in a previous radiation port)	none	faint erythema or dry desquamation	moderate to brisk erythema or a patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	confluent moist desquamation, ≥1.5 cm diameter, not confined to skin folds; pitting edema	skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma or abrasion

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Rash/desquamation	none	macular or papular eruption or erythema without associated symptoms	macular or papular eruption or erythema with pruritus or other associated symptoms covering <50% of body surface or localized desquamation or other lesions covering <50% of body surface area	symptomatic generalized erythroderma or macular, papular or vesicular eruption or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis
For BMT:	none	macular or papular eruption or erythema covering <25% of body surface area without associated symptoms	macular or papular eruption or erythema with pruritis or other associated symptoms covering ≥25 - <50% of body surface or localized desquamation or other lesions covering ≥25 - <50% of body surface area	symptomatic generalized erythroderma or symptomatic macular, papular or vesicular eruption, with bullous formation, or desquamation covering ≥50% of body surface area	generalized exfoliative dermatitis or ulcerative dermatitis or bullous formation
Also consider Allergic reaction/hypersensitivity.					
Note: Erythema multiforme (Stevens-Johnson syndrome) is graded separately as Erythema multiforme.					
Urticaria (hives, welts, wheals)	none	requiring no medication	requiring PO or topical treatment or IV medication or steroids for <24 hours	requiring IV medication or steroids for ≥24 hours	-
Wound- infectious	none	cellulitis	superficial infection	infection requiring IV antibiotics	necrotizing fascitis
Wound- non-infectious	none	incisional separation	incisional hernia	fascial disruption without evisceration	fascial disruption with evisceration
Dermatology/Skin- Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
ENDOCRINE					
Cushingoid appearance (e.g., moon face with or without buffalo hump, centripetal obesity, cutaneous striae)	absent	-	present	-	-
Also consider Hyperglycemia, Hypokalemia.					
Feminization of male	absent	-	-	present	-
Gynecomastia	none	mild	pronounced or painful	pronounced or painful and requiring surgery	-
Hot flashes/flushes	none	mild or no more than 1 per day	moderate and greater than 1 per day	-	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hypothyroidism	absent	asymptomatic,TSH elevated, no therapy given	symptomatic or thyroid replacement treatment given	patient hospitalized for manifestations of hypothyroidism	myxedema coma
Masculinization of female	absent	-	-	present	-
SIADH (syndrome of inappropriate antidiuretic hormone)	absent	-	-	present	-
Endocrine-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
GASTROINTESTINAL					
Amylase is graded in the METABOLIC/LABORATORY category.					
Anorexia	none	loss of appetite	oral intake significantly decreased	requiring IV fluids	requiring feeding tube or parenteral nutrition
Ascites (non-malignant)	none	asymptomatic	symptomatic, requiring diuretics	symptomatic, requiring therapeutic paracentesis	life-threatening physiologic consequences
Colitis	none	-	abdominal pain with mucus and/or blood in stool	abdominal pain, fever, change in bowel habits with ileus or peritoneal signs, and radiographic or biopsy documentation	perforation or requiring surgery or toxic megacolon
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Melena/GI bleeding, Rectal bleeding/hematochezia, Hypotension.					
Constipation	none	requiring stool softener or dietary modification	requiring laxatives	obstipation requiring manual evacuation or enema	obstruction or toxic megacolon
Dehydration	none	dry mucous membranes and/or diminished skin turgor	requiring IV fluid replacement (brief)	requiring IV fluid replacement (sustained)	physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Hypotension, Diarrhea, Vomiting, Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Diarrhea Patients without colostomy:	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of ≥7 stools/day or incontinence; or need for parenteral support for dehydration	physiologic consequences requiring intensive care; or hemodynamic collapse
Patients with a colostomy:	none	mild increase in loose, watery colostomy output compared with pretreatment	moderate increase in loose, watery colostomy output compared with pretreatment, but not interfering with normal activity	severe increase in loose, watery colostomy output compared with pretreatment, interfering with normal activity	physiologic consequences, requiring intensive care; or hemodynamic collapse

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
For BMT	none	>500 - ≤1000mL of diarrhea/day	>1000 - ≤1500mL of diarrhea/day	>1500mL of diarrhea/day	severe abdominal pain with or without ileus
For Pediatric BMT:		*>5 - ≤10 mL/kg of diarrhea/day*	*>10 - ≤15 mL/kg of diarrhea/day*	*>15 mL/kg of diarrhea/day*	-
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Pain, Dehydration, Hypotension.					
Duodenal ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	uncontrolled by outpatient medical management; requiring hospitalization	perforation or bleeding, requiring emergency surgery
Dyspepsia/heartburn	none	mild	moderate	severe	-
Dysphagia, esophagitis, odynophagia (painful swallowing)	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring IV hydration	complete obstruction (cannot swallow saliva) requiring enteral or parenteral nutritional support, or perforation
Note: If adverse event is radiation-related, grade either under Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation.					
Dysphagia- esophageal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft or liquid diet	dysphagia requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation.					
Note: Fistula is graded separately as Fistula- esophageal.					
Dysphagia - pharyngeal related to radiation	none	mild dysphagia, but can eat regular diet	dysphagia, requiring predominantly pureed, soft, or liquid diet	dysphagia, requiring feeding tube, IV hydration or hyperalimentation	complete obstruction (cannot swallow saliva); ulceration with bleeding not induced by minor trauma or abrasion or perforation
Also consider Pain due to radiation, Mucositis due to radiation.					
Note: Fistula is graded separately as Fistula- pharyngeal.					
Fistula- esophageal	none	-	-	present	requiring surgery
Fistula- intestinal	none	-	-	present	requiring surgery
Fistula- pharyngeal	none	-	-	present	requiring surgery
Fistula- rectal/anal	none	-	-	present	requiring surgery
Flatulence	none	mild	moderate	-	-
Gastric ulcer (requires radiographic or endoscopic documentation)	none	-	requiring medical management or non-surgical treatment	bleeding without perforation, uncontrolled by outpatient medical management; requiring hospitalization or surgery	perforation or bleeding, requiring emergency surgery

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Gastritis	none	-	requiring medical management or non-surgical treatment	uncontrolled by out-patient medical management; requiring hospitalization or surgery	life-threatening bleeding, requiring emergency surgery
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia.					
Hematemesis is graded in the HEMORRHAGE category.					
Hematochezia is graded in the HEMORRHAGE category as Rectal bleeding/hematochezia.					
Ileus (or neuroconstipation)	none	-	intermittent, not requiring intervention	requiring non-surgical intervention	requiring surgery
Mouth dryness	normal	mild	moderate	-	-
Mucositis					
Note: Mucositis not due to radiation is graded in the GASTROINTESTINAL category for specific sites: Colitis, Esophagitis, Gastritis, Stomatitis/pharyngitis (oral/pharyngeal mucositis), and Typhlitis; or the RENAL/GENITOURINARY category for Vaginititis.					
Radiation-related mucositis is graded as Mucositis due to radiation.					
Mucositis due to radiation	none	erythema of the mucosa	patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)	confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)	necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion
Also consider Pain due to radiation.					
Note: Grade radiation mucositis of the larynx here.					
Dysphagia related to radiation is also graded as either Dysphagia- esophageal related to radiation or Dysphagia- pharyngeal related to radiation, depending on the site of treatment.					
Nausea	none	able to eat	oral intake significantly decreased	no significant intake, requiring IV fluids	-
Pancreatitis	none	-	-	abdominal pain with pancreatic enzyme elevation	complicated by shock (acute circulatory failure)
Also consider Hypotension.					
Note: Amylase are graded in the METABOLIC/LABORATORY category.					
Pharyngitis is graded in the GASTROINTESTINAL category as Stomatitis/pharyngitis (oral/pharyngeal mucositis).					
Proctitis	none	increased stool frequency, occasional blood-streaked stools, or rectal discomfort (including hemorrhoids), not requiring medication	increased stool frequency, bleeding, mucus discharge, or rectal discomfort requiring medication; anal fissure	increased stool frequency/diarrhea, requiring parenteral support; rectal bleeding, requiring transfusion; or persistent mucus discharge, necessitating pads	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, and Pain due to radiation.					
Note: Fistula is graded separately as Fistula- rectal/anal.					
Proctitis occurring more than 90 days after the start of radiation therapy is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme. (See Appendix IV)					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Salivary gland changes	none	slightly thickened saliva/may have slightly altered taste (e.g., metallic); additional fluids may be required	thick, ropy, sticky saliva; markedly altered taste; alteration in diet required	-	acute salivary gland necrosis
Sense of smell	normal	slightly altered	markedly altered	-	-
Stomatitis/pharyngitis (oral/pharyngeal mucositis)	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema, or ulcers, but can eat or swallow	painful erythema, edema, or ulcers requiring IV hydration	severe ulceration or requires parenteral or enteral nutritional support or prophylatic intubation
For BMT:	none	painless ulcers, erythema, or mild soreness in the absence of lesions	painful erythema, edema or ulcers but can swallow	painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support	severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia
Note: Radiation-related mucositis is graded as Mucositis due to radiation.					
Taste disturbance (dysgeusia)	normal	slightly altered	markedly altered	-	-
Typhlitis (inflammation of the cecum)	none	-	-	abdominal pain, diarrhea, fever, and radiographic or biopsy documentation	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (e.g., colostomy)
Also consider Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia, Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia, Hypotension, Febrile/neutropenia.					
Vomiting	none	1 episode in 24 hours over pretreatment	2-5 episodes in 24 hours over pretreatment	≥6 episodes in 24 hours over pretreatment; or need for IV fluids	Requiring parenteral nutrition; or physiologic consequences requiring intensive care; hemodynamic collapse
Also consider Dehydration.					
Weight gain is graded in the CONSTITUTIONAL SYMPTOMS category.					
Weight loss is graded in the CONSTITUTIONAL SYMPTOMS category.					
Gastrointestinal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
HEMORRHAGE					
Note: Transfusion in this section refers to pRBC infusion. For any bleeding with grade 3 or 4 platelets (< 50,000), always grade Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia. Also consider platelets, transfusion: pRBCS, and Transfusion: platelets in addition to grading severity by grading the site or type of bleeding. If the site or type of Hemorrhage/bleeding is listed, also use the grading that incorporates the site of bleeding: CNS Hemorrhage/bleeding, Hematuria, Hematemesis, Hemoptysis, Hemorrhage/bleeding with surgery, Melena/lower GI bleeding, Petechiae/purpura (Hemorrhage/bleeding into skin), Rectal bleeding/hematochezia, Vaginal bleeding.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
If the platelet count is ≥50,000 and the site or type of bleeding is listed, grade the specific site. If the site or type is <u>not</u> listed and the platelet count is ≥50,000, grade Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia and specify the site or type in the OTHER category.					
Hemorrhage/bleeding with grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion: pRBCs, site or type of bleeding. If the site is not listed, grade as Hemorrhage-Other (Specify site, _____).					
Note: This adverse event must be graded for any bleeding with grade 3 or 4 thrombocytopenia.					
Hemorrhage/bleeding without grade 3 or 4 thrombocytopenia	none	mild without transfusion		requiring transfusion	catastrophic bleeding requiring major non-elective intervention
Also consider Platelets, Hemoglobin, Transfusion: platelets, Transfusion:pRBCs, Hemorrhage – Other (Specify site, _____).					
Note: Bleeding in the absence of grade 3 or 4 thrombocytopenia is graded here only if the specific site or type of bleeding is not listed elsewhere in the HEMORRHAGE category. Also grade as Other in the HEMORRHAGE category.					
CNS hemorrhage/bleeding	none	-	-	bleeding noted on CT or other scan with no clinical consequences	hemorrhagic stroke or hemorrhagic vascular event (CVA) with neurologic signs and symptoms
Epistaxis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematemesis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hematuria (in the absence of vaginal bleeding)	none	microscopic only	intermittent gross bleeding, no clots	persistent gross bleeding or clots; may require catheterization or instrumentation, or transfusion	open surgery or necrosis or deep bladder ulceration
Hemoptysis	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage/bleeding associated with surgery	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Note: Expected blood loss at the time of surgery is not graded as a toxicity.					
Melena/GI bleeding	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Petechiae/purpura (hemorrhage/bleeding into skin or mucosa)	none	rare petechiae of skin	petechiae or purpura in dependent areas of skin	generalized petechiae or purpura of skin or petechiae of any mucosal site	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Rectal bleeding/ hematochezia	none	mild without transfusion or medication	persistent, requiring medication (e.g., steroid suppositories) and/or break from radiation treatment	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Vaginal bleeding	none	spotting, requiring < 2 pads per day	requiring ≥ 2 pads per day, but not requiring transfusion	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
Hemorrhage-Other (Specify site, _____)	none	mild without transfusion	-	requiring transfusion	catastrophic bleeding, requiring major non-elective intervention
HEPATIC					
Alkaline phosphatase	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Bilirubin	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 10.0 x ULN	> 10.0 x ULN
Bilirubin- graft versus host disease (GVHD)					
Note: The following criteria are used only for bilirubin associated with graft versus host disease.					
	normal	≥2 - <3 mg/100 ml	≥3 - <6 mg/100 ml	≥6 - <15 mg/100 ml	≥15 mg/100 ml
GGT (γ - Glutamyl transpeptidase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic enlargement	absent	-	-	present	-
Note: Grade Hepatic enlargement only for treatment related adverse event including Veno-Occlusive Disease					
Hypoalbuminemia	WNL	<LLN - 3 g/dl	≥2 - <3 g/dl	<2 g/dl	-
Liver dysfunction/failure (clinical)	normal	-	-	asterixis	encephalopathy or coma
Portal vein flow	normal	-	decreased portal vein flow	reversal/retrograde portal vein flow	-
SGOT (AST) (serum glutamic oxaloacetic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
SGPT (ALT) (serum glutamic pyruvic transaminase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN
Hepatic-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
INFECTION/FEBRILE NEUTROPENIA					
Catheter-related infection	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment or hospitalization	life-threatening sepsis (e.g., septic shock)

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)	none	-	-	Present	Life-threatening sepsis (e.g., septic shock)
(ANC < 1.0 x 10^9/L, fever ≥38.5°C)					
Also consider Neutrophils Note: Hypothermia instead of fever may be associated with neutropenia and is graded here.					
Infection (documented clinically or microbiologically) with grade 3 or 4 neutropenia	none	-	-	present	life-threatening sepsis (e.g., septic shock)
(ANC < 1.0 x 10^9/L)					
Note: Hypothermia instead of fever may be associated with neutropenia and is graded here. In the absence of documented infection with grade 3 or 4 neutropenia with fever is graded as Febrile neutropenia.					
Infection with unknown ANC	none	-	-	present	life-threatening sepsis (e.g., septic shock)
Note: This adverse event criterion is used in the rare case when ANC is unknown.					
Infection without neutropenia Also consider Neutrophils	none	mild, no active treatment	moderate, localized infection, requiring local or oral treatment	severe, systemic infection, requiring IV antibiotic or antifungal treatment, or hospitalization	life-threatening sepsis (e.g., septic shock)
Infection/Febrile Neutropenia-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
Wound-infectious is graded in the DERMATOLOGY/SKIN category.					
LYMPHATICS					
Lymphatics	normal	mild lymphedema	moderate lymphedema requiring compression; lymphocyst	severe lymphedema limiting function; lymphocyst requiring surgery	severe lymphedema limiting function with ulceration
Lymphatics-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
METABOLIC/LABORATORY					
Acidosis (metabolic or respiratory)	normal	pH < normal, but ≥7.3	-	pH < 7.3	pH < 7.3 with life-threatening physiologic consequences
Alkalosis (metabolic or respiratory)	normal	pH > normal, but ≤7.5	-	pH > 7.5	pH > 7.5 with life-threatening physiologic consequences
Amylase Bicarbonate	WNL WNL	> ULN - 1.5 x ULN < LLN - 16 mEq/dl	> 1.5 - 2.0 x ULN 11 - 15 mEq/dl	> 2.0 - 5.0 x ULN 8 - 10 mEq/dl	>5.0 x ULN < 8 mEq/dl

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
CPK (creatine phosphokinase)	WNL	> ULN - 2.5 x ULN	> 2.5 - 5 x ULN	> 5 - 10 x ULN	> 10 x ULN
Hypercalcemia	WNL	> ULN - 11.5 mg/dl > ULN - 2.9 mmol/L	>11.5 - 12.5 mg/dl > 2.9 - 3.1 mmol/L	>12.5 - 13.5 mg/dl > 3.1 - 3.4 mmol/L	> 13.5 mg/dl > 3.4 mmol/L
Hypercholesterolemia	WNL	> ULN - 300 mg/dl > ULN - 7.75 mmol/L	> 300 - 400 mg/dl > 7.75 - 10.34 mmol/L	> 400 - 500 mg/dl >10.34 - 12.92 mmol/L	> 500 mg/dl > 12.92 mmol/L
Hyperglycemia	WNL	> ULN - 160 mg/dl > ULN - 8.9 mmol/L	> 160 - 250 mg/dl > 8.9 - 13.9 mmol/L	> 250 - 500 mg/dl > 13.9 - 27.8 mmol/L	> 500 mg/dl > 27.8 mmol/L or ketoacidosis
Hyperkalemia	WNL	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L
Hypermagnesemia	WNL	> ULN - 3.0 mg/dl > ULN - 1.23 mmol/L	-	> 3.0 - 8.0 mg/dl > 1.23 - 3.30 mmol/L	> 8.0 mg/dl > 3.30 mmol/L
Hypernatremia	WNL	> ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L	>160 mmol/L
Hypertriglyceridemia	WNL	> ULN - 2.5 x ULN	> 2.5 - 5.0 x ULN	> 5.0 - 10 x ULN	> 10 x ULN
Hyperuricemia	WNL	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L without physiologic consequences	-	> ULN - ≤ 10 mg/dl ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dl > 0.59 mmol/L
Also consider Tumor lysis syndrome, Renal failure, Creatinine,Hyperkalemia.					
Hypocalcemia	WNL	<LLN - 8.0 mg/dl <LLN - 2.0 mmol/L	7.0 - < 8.0 mg/dl 1.75 - < 2.0 mmol/L	6.0 - < 7.0 mg/dl 1.5 - < 1.75 mmol/L	<6.0 mg/dl < 1.5 mmol/L
Hypoglycemia	WNL	<LLN - 55 mg/dl <LLN - 3.0 mmol/L	40 - < 55 mg/dl 2.2 - < 3.0 mmol/L	30 - < 40 mg/dl 1.7 - < 2.2 mmol/L	< 30 mg/dl < 1.7 mmol/L
Hypokalemia	WNL	<LLN - 3.0 mmol/L	-	2.5 - <3.0 mmol/L	<2.5 mmol/L
Hypomagnesemia	WNL	<LLN - 1.2 mg/dl <LLN - 0.5 mmol/L	0.9 - <1.2 mg/dl 0.4 - < 0.5 mmol/L	0.7 - < 0.9 mg/dl 0.3 - < 0.4 mmol/L	< 0.7 mg/dl < 0.3 mmol/L
Hyponatremia	WNL	<LLN - 130 mmol/L	-	120 - <130 mmol/L	<120 mmol/L
Hypophosphatemia	WNL	<LLN -2.5 mg/dl <LLN - 0.8 mmol/L	≥2.0 - <2.5 mg/dl ≥0.6 - <0.8 mmol/L	≥1.0 - <2.0 mg/dl ≥0.3 - <0.6 mmol/L	< 1.0 mg/dl <0.3 mmol/L
Hypothyroidism is graded in the ENDOCRINE category.					
Lipase	WNL	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Metabolic/Laboratory-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
MUSCULOSKELETAL					
Arthralgia is graded in the PAIN category.					
Arthritis	none	mild pain with inflammation, erythema or joint swelling but not interfering with function	moderate pain with inflammation, erythema, or joint swelling interfering with function, but not interfering with activities of daily living	severe pain with inflammation, erythema, or joint swelling and interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Muscle weakness (not due to neuropathy)	normal	asymptomatic with weakness on physical exam	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	bedridden or disabling
Myalgia [tenderness or pain in muscles] is graded in the PAIN category.					
Myositis (inflammation/damage of muscle)	none	mild pain, not interfering with function	pain interfering with function, but not interfering with activities of daily living	pain interfering with function and interfering with activities of daily living	bedridden or disabling
Also consider CPK.					
Note: Myositis implies muscle damage (i.e., elevated CPK).					
Osteonecrosis (avascular necrosis)	none	asymptomatic and detected by imaging only	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	symptomatic; or disabling
Musculoskeletal-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
NEUROLOGY					
Aphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Arachnoiditis/meningismus/ radiculitis	absent	mild pain not interfering with function	moderate pain interfering with function, but not interfering with activities of daily living	severe pain interfering with activities of daily living	unable to function or perform activities of daily living; bedridden; paraplegia
Also consider Headache, Vomiting, Fever.					
Ataxia (incoordination)	normal	asymptomatic but abnormal on physical exam, and not interfering with function	mild symptoms interfering with function, but not interfering with activities of daily living	moderate symptoms interfering with activities of daily living	bedridden or disabling
CNS cerebrovascular ischemia	none	-	-	transient ischemic event or attack (TIA)	permanent event (e.g., cerebral vascular accident)
CNS hemorrhage/bleeding is graded in the HEMORRHAGE category.					
Cognitive disturbance/ learning problems	*none*	*cognitive disability; not interfering with work/school performance; preservation of intelligence*	*cognitive disability; interfering with work/school performance; decline of 1 SD (Standard Deviation) or loss of developmental milestones*	*cognitive disability; resulting in significant impairment of work/school performance; cognitive decline > 2 SD*	*inability to work/frank mental retardation*

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Confusion	normal	confusion or disorientation or attention deficit of brief duration; resolves spontaneously with no sequelae	confusion or disorientation or attention deficit interfering with function, but not interfering with activities of daily living	confusion or delirium interfering with activities of daily living	harmful to others or self; requiring hospitalization
Cranial neuropathy is graded in the NEUROLOGY category as Neuropathy-cranial.					
Delusions	normal	-	-	present	toxic psychosis
Depressed level of consciousness	normal	somnolence or sedation not interfering with function	somnolence or sedation interfering with function, but not interfering with activities of daily living	obtundation or stupor; difficult to arouse; interfering with activities of daily living	coma
Note: Syncope (fainting) is graded in the NEUROLOGY category.					
Dizziness/lightheadedness	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Dysphasia, receptive and/or expressive, is graded under Speech impairment in the NEUROLOGY category.					
Extrapyramidal/ involuntary movement/ restlessness	none	mild involuntary movements not interfering with function	moderate involuntary movements interfering with function, but not interfering with activities of daily living	severe involuntary movements or torticollis interfering with activities of daily living	bedridden or disabling
Hallucinations	normal	-	-	present	toxic psychosis
Headache is graded in the PAIN category.					
Insomnia	normal	occasional difficulty sleeping not interfering with function	difficulty sleeping interfering with function, but not interfering with activities of daily living	frequent difficulty sleeping, interfering with activities of daily living	-
Note: This toxicity is graded when insomnia is related to treatment. If pain or other symptoms interfere with sleep do NOT grade as insomnia.					
Irritability *(children <3 years of age)*	*normal*	*mild; easily consolable*	*moderate; requiring increased attention*	*severe; inconsolable*	-
Leukoencephalopathy associated radiological findings	*none*	*mild increase in SAS (subarachnoid space) and/or mild ventriculomegaly; and/or small (+/- multiple) focal T2 hyperintensities, involving periventricular white matter or < 1/3 of susceptible areas of cerebrum*	*moderate increase in SAS; and/or moderate ventriculomegaly; and/or focal T2 hyperintensities extending into centrum ovale; or involving 1/3 to 2/3 of susceptible areas of cerebrum*	*severe increase in SAS; severe ventriculomegaly; near total white matter T2 hyperintensities or diffuse low attenuation (CT); focal white matter necrosis (cystic)*	*severe increase in SAS; severe ventriculomegaly; diffuse low attenuation with calcification (CT); diffuse white matter necrosis (MRI)*

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Memory loss	normal	memory loss not interfering with function	memory loss interfering with function, but not interfering with activities of daily living	memory loss interfering with activities of daily living	amnesia
Mood alteration-anxiety agitation	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-depression	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	suicidal ideation or danger to self
Mood alteration-euphoria	normal	mild mood alteration not interfering with function	moderate mood alteration interfering with function, but not interfering with activities of daily living	severe mood alteration interfering with activities of daily living	danger to self
Neuropathic pain is graded in the PAIN category.					
Neuropathy- cranial	absent	-	present, not interfering with activities of daily living	present, interfering with activities of daily living	life-threatening, disabling
Neuropathy- motor	normal	subjective weakness but no objective findings	mild objective weakness interfering with function, but not interfering with activities of daily living	objective weakness interfering with activities of daily living	paralysis
Neuropathy-sensory	normal	loss of deep tendon reflexes or paresthesia (including tingling) but not interfering with function	objective sensory loss or paresthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paresthesia interfering with activities of daily living	permanent sensory loss that interferes with function
Nystagmus	absent	present	-	-	-
Also consider Vision-double vision.					
Personality/behavioral	normal	change, but not disruptive to patient or family	disruptive to patient or family	disruptive to patient and family; requiring mental health intervention	harmful to others or self; requiring hospitalization

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Pyramidal tract dysfunction (e.g., ↑ tone, hyperreflexia, positive Babinski, ↓ fine motor coordination)	normal	asymptomatic with abnormality on physical examination	symptomatic or interfering with function but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling; paralysis
Seizure(s)	none	-	seizure(s) self-limited and consciousness is preserved	seizure(s) in which consciousness is altered	seizures of any type which are prolonged, repetitive, or difficult to control (e.g., status epilepticus, intractable epilepsy)
Speech impairment (e.g., dysphasia or aphasia)	normal	-	awareness of receptive or expressive dysphasia, not impairing ability to communicate	receptive or expressive dysphasia, impairing ability to communicate	inability to communicate
Syncope (fainting)	absent	-	-	present	-
Also consider CARDIOVASCULAR (ARRHYTHMIA), Vasovagal episode, CNS cerebrovascular ischemia.					
Tremor	none	mild and brief or intermittent but not interfering with function	moderate tremor interfering with function, but not interfering with activities of daily living	severe tremor interfering with activities of daily living	-
Vertigo	none	not interfering with function	interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	bedridden or disabling
Neurology-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
OCULAR/VISUAL					
Cataract	none	asymptomatic	symptomatic, partial visual loss	symptomatic, visual loss requiring treatment or interfering with function	-
Conjunctivitis	none	abnormal ophthalmologic changes, but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Dry eye	normal	mild, not requiring treatment	moderate or requiring artificial tears	-	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Glaucoma	none	increase in intraocular pressure but no visual loss	increase in intraocular pressure with retinal changes	visual impairment	unilateral or bilateral loss of vision (blindness)
Keratitis (corneal inflammation/ corneal ulceration)	none	abnormal ophthalmologic changes but asymptomatic or symptomatic without visual impairment (i.e., pain and irritation)	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	unilateral or bilateral loss of vision (blindness)
Tearing (watery eyes)	none	mild: not interfering with function	moderate: interfering with function, but not interfering with activities of daily living	interfering with activities of daily living	-
Vision- blurred vision	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- double vision (diplopia)	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- flashing lights/floaters	normal	mild, not interfering with function	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- night blindness (nyctalopia)	normal	abnormal electro-retinography but asymptomatic	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Vision- photophobia	normal	-	symptomatic and interfering with function, but not interfering with activities of daily living	symptomatic and interfering with activities of daily living	-
Ocular/Visual-Other (Specify, _____)	normal	mild	moderate	severe	unilateral or bilateral loss of vision (blindness)
PAIN					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Abdominal pain or cramping	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthralgia (joint pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Arthritis (joint pain with clinical signs of inflammation) is graded in the MUSCULOSKELETAL category.					
Bone pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Chest pain (non-cardiac and non-pleuritic)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dysmenorrhea	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Dyspareunia	none	mild pain not interfering with function	moderate pain interfering with sexual activity	severe pain preventing sexual activity	-
Dysuria is graded in the RENAL/GENITOURINARY category.					
Earache (otalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Headache	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Hepatic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Myalgia (muscle pain)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Neuropathic pain (e.g., jaw pain, neurologic pain, phantom limb pain, post-infectious neuralgia, or painful neuropathies)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pain due to radiation	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pelvic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Pleuritic pain	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor pain (onset or exacerbation of tumor pain due to treatment)	none	mild pain not interfering with function	moderate pain: pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain: pain or analgesics severely interfering with activities of daily living	disabling
Tumor flair is graded in the SYNDROME category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Pain-Other (Specify, _____)	none	mild	moderate	severe	disabling
PULMONARY					
Adult Respiratory Distress Syndrome (ARDS)	absent	-	-	-	present
Apnea	none	-	-	present	requiring intubation
Carbon monoxide diffusion capacity (DL_{CO})	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Cough	absent	mild, relieved by non-prescription medication	requiring narcotic antitussive	severe cough or coughing spasms, poorly controlled or unresponsive to treatment	-
Dyspnea (shortness of breath)	normal	-	dyspnea on exertion	dyspnea at normal level of activity	dyspnea at rest or requiring ventilator support
FEV_1	≥ 90% of pretreatment or normal value	≥75 - <90% of pretreatment or normal value	≥50 - <75% of pretreatment or normal value	≥25 - <50% of pretreatment or normal value	< 25% of pretreatment or normal value
Hiccoughs (hiccups, singultus)	none	mild, not requiring treatment	moderate, requiring treatment	severe, prolonged, and refractory to treatment	-
Hypoxia	normal	-	decreased O_2 saturation with exercise	decreased O_2 saturation at rest, requiring supplemental oxygen	decreased O_2 saturation, requiring pressure support (CPAP) or assisted ventilation
Pleural effusion (non-malignant)	none	asymptomatic and not requiring treatment	symptomatic, requiring diuretics	symptomatic, requiring O_2 or therapeutic thoracentesis	life-threatening (e.g., requiring intubation)
Pleuritic pain is graded in the PAIN category.					
Pneumonitis/pulmonary infiltrates	none	radiographic changes but asymptomatic or symptoms not requiring steroids	radiographic changes and requiring steroids or diuretics	radiographic changes and requiring oxygen	radiographic changes and requiring assisted ventilation
Pneumothorax	none	no intervention required	chest tube required	sclerosis or surgery required	life-threatening
Pulmonary embolism is graded as Thrombosis/embolism in the CARDIOVASCULAR (GENERAL) category.					
Pulmonary fibrosis	none	radiographic changes, but asymptomatic or symptoms not requiring steroids	requiring steroids or diuretics	requiring oxygen	requiring assisted ventilation
Note: Radiation-related pulmonary fibrosis is graded in the RTOG/EORTC Late Radiation Morbidity Scoring Scheme- Lung. (See Appendix IV)					
Voice changes/stridor/larynx (e.g., hoarseness, loss of voice, laryngitis)	normal	mild or intermittent hoarseness	persistent hoarseness, but able to vocalize; may have mild to moderate edema	whispered speech, not able to vocalize; may have marked edema	marked dyspnea/stridor requiring tracheostomy or intubation
Note: Cough from radiation is graded as cough in the PULMONARY category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Radiation-related hemoptysis from larynx/pharynx is graded as Grade 4 Mucositis due to radiation in the GASTROINTESTINAL category. Radiation-related hemoptysis from the thoracic cavity is graded as Grade 4 Hemoptysis in the HEMORRHAGE category.					
Pulmonary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
RENAL/GENITOURINARY					
Bladder spasms	absent	mild symptoms, not requiring intervention	symptoms requiring antispasmotic	severe symptoms requiring narcotic	-
Creatinine	WNL	> ULN - 1.5 x ULN	> 1.5 - 3.0 x ULN	> 3.0 - 6.0 x ULN	> 6.0 x ULN
Note: Adjust to age-appropriate levels for pediatric patients.					
Dysuria (painful urination)	none	mild symptoms requiring no intervention	symptoms relieved with therapy	symptoms not relieved despite therapy	-
Fistula or GU fistula (e.g., vaginal, vesicovaginal)	none	-	-	requiring intervention	requiring surgery
Hemoglobinuria	-	present	-	-	-
Hematuria (in the absence of vaginal bleeding) is graded in the HEMORRHAGE category.					
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-
Operative injury to bladder and/or ureter	none	-	injury of bladder with primary repair	sepsis, fistula, or obstruction requiring secondary surgery; loss of one kidney; injury requiring anastomosis or re-implantation	septic obstruction of both kidneys or vesicovaginal fistula requiring diversion
Proteinuria	normal or < 0.15 g/24 hours	1+ or 0.15 - 1.0 g/24 hours	2+ to 3+ or 1.0 - 3.5 g/24 hours	4+ or > 3.5 g/24 hours	nephrotic syndrome
Note: If there is an inconsistency between absolute value and dip stick reading, use the absolute value for grading.					
Renal failure	none	-	-	requiring dialysis, but reversible	requiring dialysis and irreversible
Ureteral obstruction	none	unilateral, not requiring surgery	-	bilateral, not requiring surgery	stent, nephrostomy tube, or surgery
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis)	none	asymptomatic, not requiring treatment	mild, reversible and manageable with oral replacement	reversible but requiring IV replacement	irreversible, requiring continued replacement
Also consider Acidosis, Bicarbonate, Hypocalcemia, Hypophosphatemia.					
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x normal	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	-

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine; retention occurring during the immediate postoperative period	hesitancy requiring medication or occasional in/out catheterization (<4 x per week), or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks	requiring frequent in/out catheterization (≥ 4 x per week) or urological intervention (e.g., TURP, suprapubic tube, urethrotomy)	bladder rupture
Urine color change (not related to other dietary or physiologic cause e.g., bilirubin, concentrated urine, hematuria)	normal	asymptomatic, change in urine color	-	-	-
Vaginal bleeding is graded in the HEMORRHAGE category.					
Vaginitis (not due to infection)	none	mild, not requiring treatment	moderate, relieved with treatment	severe, not relieved with treatment, or ulceration not requiring surgery	ulceration requiring surgery
Renal/Genitourinary-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling
SECONDARY MALIGNANCY					
Secondary Malignancy-Other (Specify type, _____) excludes metastastic tumors	none	-	-	-	present
SEXUAL/REPRODUCTIVE FUNCTION					
Dyspareunia is graded in the PAIN category.					
Dysmenorrhea is graded in the PAIN category.					
Erectile impotence	normal	mild (erections impaired but satisfactory)	moderate (erections impaired, unsatisfactory for intercourse)	no erections	-
Female sterility	normal	-	-	sterile	-
Femininization of male is graded in the ENDOCRINE category.					
Irregular menses (change from baseline)	normal	occasionally irregular or lengthened interval, but continuing menstrual cycles	very irregular, but continuing menstrual cycles	persistent amenorrhea	-
Libido	normal	decrease in interest	severe loss of interest	-	-
Male infertility	-	-	Oligospermia (low sperm count)	Azoospermia (no sperm)	-
Masculinization of female is graded in the ENDOCRINE category.					

	Grade				
Adverse Event	**0**	**1**	**2**	**3**	**4**
Vaginal dryness	normal	mild	requiring treatment and/or interfering with sexual function, dyspareunia	-	-
Sexual/Reproductive Function-Other (Specify, _____)	none	mild	moderate	severe	disabling
SYNDROMES (not included in previous categories)					
Acute vascular leak syndrome is graded in the CARDIOVASCULAR (GENERAL) category.					
ARDS (Adult Respiratory Distress Syndrome) is graded in the PULMONARY category.					
Autoimmune reactions are graded in the ALLERGY/IMMUNOLOGY category.					
DIC (disseminated intravascular coagulation) is graded in the COAGULATION category.					
Fanconi's syndrome is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Renal tubular acidosis is graded as Urinary electrolyte wasting in the RENAL/GENITOURINARY category.					
Stevens-Johnson syndrome (erythema multiforme) is graded in the DERMATOLOGY/SKIN category.					
SIADH (syndrome of inappropriate antidiuretic hormone) is graded in the ENDOCRINE category.					
Thrombotic microangiopathy (e.g., thromboitic thrombocytopenic purpura/TTP or hemolytic uremic syndrom/HUS) is graded in the COAGULATION category.					
Tumor flare	none	mild pain not interfering with function	moderate pain; pain or analgesics interfering with function, but not interfering with activities of daily living	severe pain; pain or analgesics interfering with function and interfering with activities of daily living	Disabling
Also consider Hypercalcemia.					
Note: Tumor flare is characterized by a constellation of symptoms and signs in direct relation to initiation of therapy (e.g., anti-estrogens/androgens or additional hormones). The symptoms/signs include tumor pain, inflammation of visible tumor, hypercalcemia, diffuse bone pain, and other electrolyte disturbances.					
Tumor lysis syndrome	absent	-	-	present	-
Also consider Hyperkalemia, Creatinine.					
Urinary electrolyte wasting (e.g., Fanconi's syndrome, renal tubular acidosis) is graded in the RENAL/GENITOURINARY category.					
Syndromes-Other (Specify, _____)	none	mild	moderate	severe	life-threatening or disabling